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Rapportage van de Externe Evaluatiecommissie GGG

INHOUD

1. Inleiding

In 2017 is het ZonMw programma Goed Gebruik Geneesmiddelen (GGG) vijf jaar onderweg. Met het ministerie van Volksgezondheid, Welzijn en Sport (VWS) is afgesproken dat er na die vijf jaar een eerste evaluatie zal plaatsvinden. Deze tussentijdse evaluatie bestaat uit twee delen, te weten een proces- en uitkomstevaluatie, uitgevoerd door Technopolis, neergelegd in het rapport 'Interim evaluation of the Rational Pharmacotherapy (GGG-) Programme' (bijlage 1) en een rapportage van de Externe Evaluatiecommissie (zie bijlage 2 voor samenstelling en mandaat van deze commissie), waarbij op genoemde proces- en uitkomstevaluatie wordt gereflecteerd. In deze rapportage markeert en becommentarieert de Externe Evaluatiecommissie een aantal bevindingen uit het evaluatieonderzoek uitgevoerd door Technopolis. Deze reflecties geven, gelet op het interim karakter van deze evaluatie, uiteraard een voorlopige stand van zaken weer. De rapportage wordt afgesloten met een aantal aanbevelingen.

2. Werkwijze van de Externe Evaluatiecommissie

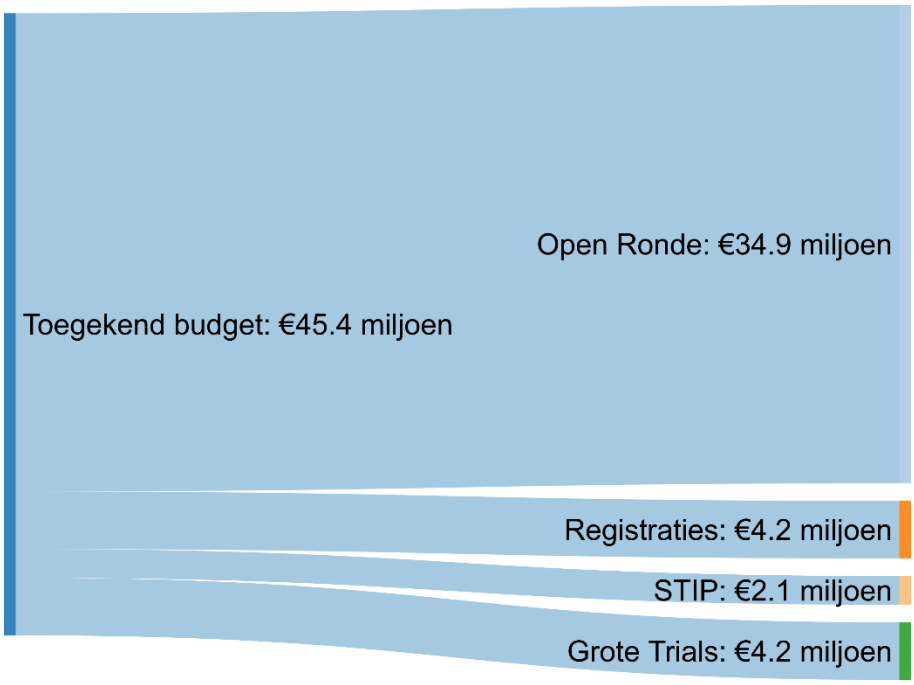
De eerste bijeenkomst van de Externe Evaluatiecommissie was op 6 februari 2017 met het ZonMw GGG-secretariaat. Op deze bijeenkomst zijn de '*Terms of reference'* voor de proces- en uitkomstevaluatie geformuleerd. De ontvangen offertes voor uitvoering van de evaluatie zijn op 20 maart beoordeeld, waarbij de opdracht is gegund aan Technopolis. Op de derde bijeenkomst (11 april 2017) zijn de doelstellingen en werkwijze van de proces- en resultaatevaluatie in meer detail met Technopolis besproken. In de twee volgende bijeenkomsten (16 mei 2017 en 28 juni 2017) is de voortgang van de evaluatie geagendeerd, waarna op 13 september en 25 oktober 2017 conceptversies van het rapport zijn besproken.

3. Reflecties naar aanleiding van het evaluatierapport van Technopolis

De Externe Evaluatiecommissie spreekt haar waardering uit voor de werkwijze, verrichte analyses en rapportage door Technopolis. Het rapport geeft een schat aan informatie over zowel het proces, de uitkomsten tot dusverre, de gemaakte keuzes door ZonMw, als de actuele vormgeving van het GGG-programma.

3.1. Algemeen

Het ZonMw programma Goed Gebruik Geneesmiddelen (GGG) is een ambitieus en strategisch belangrijk onderzoeksprogramma dat relevante vraagstellingen en leemtes in de kennis over het juiste gebruik van geneesmiddelen in de klinische praktijk zichtbaar maakt en onderzoekt. Na een uitvoerige selectieprocedure door ZonMw worden deze vraagstellingen en leemtes (voor een deel) vertaald in een omvangrijk pakket aan onderzoeksprojecten uitgevoerd binnen de Nederlandse kennisinfrastructuur (universiteiten, ziekenhuizen, andere instituten). In totaal zijn over de periode 2012-mei 2017, in 12 rondes (zogenoemde *calls*) 1.027 projectideeën op het gebied van GGG ontvangen. Daarvan zijn er, na een selectieprocedure door ZonMw, 377 uitgewerkt in projectvoorstellen. Hiervan zijn er uiteindelijk 142 geselecteerd om uit te voeren.
De Externe Evaluatiecommissie onderschrijft de bevindingen van Technopolis wat betreft de grote professionaliteit en deskundigheid van het GGG-secretariaat, de sterke interacties met de onderzoeksomgeving en het hoge ambitieniveau.
Het programma bestaat uit verschillende delen, op hoofdlijnen een Open Ronde en op basis van input van *stakeholders* (via de GGG-Raad, VWS, etc.) verschillende meer gerichte deelprogramma's (Registraties, STIP, Grote Trials, Rediscovery, Personalised Medicine).
Op het moment van de evaluatie door Technopolis (peildatum dataverzameling voorjaar 2017) waren er 14 projecten afgerond en bevonden zich 128 projecten in een fase van uitvoering. In totaal was er toen reeds 45 miljoen Euro toegekend. Het hoofdprogramma (Open Ronde) besloeg ongeveer driekwart van de gefinancierde projecten (zie Figuur 1).



Figuur 1. Toegekende budgetten (voorjaar 2017) naar deelprogramma in miljoenen €

3.2. Interactie met en inbreng vanuit veldpartijen (stakeholders)

De wijze waarop verschillende *stakeholders* (zorginstellingen, zorgverleners, patiënten, verzekeraars, industrie), onder andere via de GGG-raad, betrokken worden bij het programma is uniek. De Externe Evaluatiecommissie is van oordeel dat een dergelijk model, op het moment van deze evaluatie nog zeker niet volmaakt en nog in ontwikkeling, verdere steun verdient. Een thema als GGG is immers multidisciplinair, kent verschillende belangen en perspectieven, en komt het best tot ontwikkeling in samenwerking met veldpartijen.
De Externe Evaluatiecommissie onderkent dat de *bottom-up* aanpak in met name de Open Ronde als consequentie heeft dat er minder regie was op de keuze van de onderzoeksvragen. Dit heeft geleid tot een oververtegenwoordiging of juist ondervertegenwoordiging van bepaalde veldpartijen en onderzoeksdisciplines, als ook tot fragmentatie van onderzoeksvragen.
De GGG-Raad heeft een belangrijke sturende rol gespeeld in het opzetten van gerichte deelprogramma's, zoals Personalised Medicine (aangereikt door de zorgverzekeraars, nog niet meegenomen in deze evaluatie) of STIP (naar aanleiding van de vaststelling dat er onvoldoende mogelijkheden waren om verworven kennis te implementeren in de dagelijkse praktijk). Het onderzoek van Technopolis laat duidelijk zien dat door deze uitbreidingen naar gerichte deelprogramma's, er vraaggestuurde dynamiek is gerealiseerd. Vanuit het onderzoeksveld is deze dynamiek positief ontvangen. Toch lijkt bezinning over de samenstelling en de werkwijze van de GGG-raad wenselijk. Zijn alle relevante *stakeholders* voldoende vertegenwoordigd en is er voldoende aansluiting bij de praktische problemen die in het zorg- en onderzoeksveld spelen?

De Externe Evaluatiecommissie erkent de inspanningen die zijn gedaan om de patiënt/eindgebruiker bij de aansturing van het programma, de selectie en uitvoering van de projecten adequaat te betrekken. Hoewel in de samenstelling van de GGG-raad voorzien is in interactie met de patiënt/eindgebruiker, en projectvoorstellen mede beoordeeld worden door een patiëntenpanel, kan effectieve betrokkenheid van de patiënt/eindgebruiker nog verder versterkt worden, bijvoorbeeld door het patiëntenpanel ook bij de monitoring en het faciliteren van de onderzoeksprojecten te betrekken.
Daarnaast was er ook op financieel gebied samenwerking met en participatie van private partijen in het GGG-programma voorzien. Dit heeft op projectniveau tot dus ver slechts marginaal plaatsgevonden. Het beoogde *multiplier* effect is hierdoor (nog) niet gerealiseerd. Uit het onderzoek van Technopolis komt een beeld naar voren dat de farmaceutische industrie nog zoekt naar de toegevoegde waarde van (financiële) participatie in het GGG-programma. Het lijkt te ontbreken aan een aansprekende industrie-brede *business case*. Bij zorgverzekeraars wordt het gebrek aan non-concurrentieel geld als belangrijke belemmerende factor benoemd.

3.3. Selectieprocedure van de projecten

Voor het selecteren van de onderzoeksvoorstellen voor het GGG-programma is door ZonMw een uitvoerig systeem van beoordelen, wegen en besluiten geïmplementeerd. Het onderzoek van Technopolis geeft diverse overzichten van de aard van de aanvragers, de inhoudelijke gebieden en de slaagkansen. Voor de Open Ronde (ongeveer driekwart van de bestedingen) waren de slaagkansen voor een positieve honorering de afgelopen vijf jaar 11%, respectievelijk 17% (bij herindiening). Het viel de Externe Evaluatiecommissie op dat projecten met een robuuste methodologie, hoge interne validiteit (RCTs, etc.) en snel aantoonbare impact, relatief vaak werden geselecteerd. Projecten met een niet-experimenteel karakter en een meer brede en praktische betekenis op langere termijn, leken minder kansrijk te zijn.

Het lijkt de commissie nog te vroeg om vergaande uitspraken over de slaagkansen en de inhoudelijke keuzes voor de STIP, Registraties en de Grote Trials deelprogramma's . Dit zijn ambitieuze deelprogramma's en het is goed dat daar een passende leercurve wordt betracht, zoals eerder benoemd.
Het onderzoek van Technopolis roept tevens een beeld op dat de vraagsteller, de onderzoeker, respectievelijk de gebruiker van de nieuwe kennis, vaak niet dezelfde partijen of personen zijn. In de selectieprocedures lijkt de onderzoeker, met een sterke rol voor de methodologische robuustheid, primair leidend te zijn.
De Externe Evaluatiecommissie stelt met enige zorg vast dat met name de universitair medische centra en universiteiten de primaire aanvragers en uitvoerders binnen het GGG-programma blijken te zijn. Deze partijen hebben doorgaans de methodologische expertise (en tijd) om kansrijke projectvoorstellen in te dienen. Hoewel het onderzoek van Technopolis laat zien dat er in een aantal gevallen ook andere organisaties, zoals de eerstelijnszorg, onderdeel zijn van een projectgroep, dient voor oververtegenwoordiging van de specialistische zorg in het GGG-programma gewaakt worden. Te meer daar 80% van alle geneesmiddelen worden gebruikt in de eerste lijn waar ook veel van de GGG-prioriteiten liggen.

Tijdens de looptijd van deze evaluatie (2012-2017) zijn de eisen wat betreft mogelijke conflicterende belangen die door ZonMw gesteld worden aan de samenstelling en werkwijze van de programmacommissies verder aangescherpt. In de media is over de toedracht daarvan onlangs ruim aandacht geweest. De Externe Evaluatiecommissie heeft hier zelf geen nader onderzoek naar verricht, maar vertrouwt erop dat de code Belangverstrengeling wordt nageleefd. De commissie wil benadrukken dat belangenverstrengeling bij de toekenning van onderzoeksgelden absoluut moet worden voorkomen. Tegelijkertijd is het van belang dat diversiteit en expertise in de programmacommissies moeten worden gewaarborgd.

3.4. Inhoudelijke invulling

Het GGG-programma heeft als doelstelling onderzoek te financieren waarin openstaande vragen op het gebied van goed geneesmiddelengebruik centraal staan. Bij het ontwerp van het programma zijn die vragen gegroepeerd in een aantal thema's, ook wel kamers van het GGG-huis genoemd, te weten 'effectiviteit en doelmatigheid', 'therapie op maat', 'andere indicaties' en 'therapietrouw en polyfarmacie'. Welke invulling hier inhoudelijk aan gegeven wordt, respectievelijk kan worden, is afhankelijk van de aanwezige kennisinfrastructuur in Nederland op het gebied van deze thema's, de onderzoeksideeën die worden ingediend en het selectieproces door ZonMw. Uit het onderzoek van Technopolis blijkt dat op al deze thema's projecten zijn gehonoreerd, al is de verdeling over de thema's niet evenredig. Het merendeel van de tot dusver gehonoreerde projecten betreft het thema 'effectiviteit en doelmatigheid', vrijwel geheel binnen de Open Ronde. Wat betreft klinische domeinen is er vooral veel onderzoeksgeld gegaan naar het cardiovasculaire domein en naar het domein van de geestelijke gezondheid (psychiatrie).
De Externe Evaluatiecommissie juicht toe dat er zoveel projecten gericht op het vullen van klinische relevante leemtes in geneesmiddelenkennis zijn gehonoreerd, kennis die noodzakelijk is voor een goed gebruik van deze middelen. Tegelijkertijd roept die oververtegenwoordiging van 'effectiviteit en doelmatigheid' projecten wel vragen op. Waar het onderzoek betreft met geneesmiddelen die reeds uit octrooi zijn, is het goed te verantwoorden dat deze vragen met publiek geld worden beantwoord. Gaat het om goed gebruik van nieuwe geneesmiddelen dan zou daarvoor ook een verantwoordelijkheid liggen bij de producenten van deze producten.
De Externe Evaluatiecommissie constateert ook een ondervertegenwoordiging van projecten op het gebied van 'therapietrouw en polyfarmacie'; hetzelfde geldt voor 'farmacotherapie bij ouderen'. Dit wordt als een gemis ervaren gezien de grote impact van deze thema's op het goed geneesmiddelengebruik in algemene zin. De commissie is van mening dat nader zou moet worden onderzocht wat hiervan de reden is en hoe binnen het programma hier verbetering in kan worden gebracht. Mogelijk is een van de redenen dat onderzoek naar 'polyfarmacie en therapietrouw' methodologisch complex is. In dat geval is een wetenschappelijke voorstudie voor geschikte methodologieën voor dit type onderzoek aan te bevelen.
Uit het onderzoek van Technopolis komt een beeld naar voren dat het laveren tussen het brede open karakter van de Open Ronde en een meer gerichte thematische, *top-down* sturing, een dilemma blijft. Er is eerder in deze rapportage gewezen op het risico van fragmentatie en gebrek aan samenhang door de

primaire *bottom-up* insteek van het programma. Nu ook blijkt dat belangrijke GGG-thema's onderbelicht blijven, lijkt een bezinning op de regierol en pro-activiteit, onder andere van de GGG-raad, in dat kader wenselijk.

3.5. Implementeerbaarheid

De Externe Evaluatiecommissie heeft uitvoerig stil gestaan bij de mate en wijze van implementeerbaarheid van de resultaten van het GGG-programma. Succes van het programma ligt in het daadwerkelijk veranderen en verbeteren van de praktijk rondom het gebruik en toepassing van geneesmiddelen. Voor een vergaand oordeel daarover is het gelet op het interim karakter van deze evaluatie nog te vroeg, maar de commissie wil hier wel verschillende knelpunten benoemen.
In de selectieprocedure van ZonMw is implementeerbaarheid van de verworven kennis één van de criteria, maar implementatie als zodanig mag geen doelstelling of onderdeel zijn van het voorstel. In de opdrachtbrief van het ministerie van VWS[1] is expliciet gesteld dat het GGG-programma niet bedoeld is voor daadwerkelijke implementatie van de verkregen kennis in de beroepspraktijk. Het GGG-programma dient in algemene zin aandacht aan implementatie te besteden en zorg te dragen dat kennis beschikbaar komt en wordt verspreid. Vooralsnog laat de evaluatie van Technopolis zien dat implementatiekracht van het programma beperkt is, of nog onvoldoende zichtbaar is indien wel aanwezig. De Externe Evaluatiecommissie stelt vast dat hier een voortdurende spanning bestaat tussen enerzijds de gestelde randvoorwaarden van het ZonMw programma, en anderzijds de gewenste impact van het programma in de praktijk.
Om tot effectieve implementatie te komen blijft het noodzakelijk om te zoeken naar manieren om de aansluiting van de resultaten van projecten bij de behoefte van het veld te verbeteren. Hiervoor kan gekeken worden naar een betere afstemming tussen het onderzoeksveld en het zorgveld vooraf, dus tijdens de aanvraag en selectie van onderzoeksvoorstellen. Maar ook achteraf bijvoorbeeld in de vorm van presentatie van resultaten die opgepakt kunnen worden door degenen die implementatie wel kunnen bewerkstelligen, zoals bijvoorbeeld de diverse *stakeholders* uit de GGG-raad. De Externe Evaluatiecommissie wil benadrukken dat het onderzoek bij voorkeur moet zijn ingebed in een implementatietraject en niet op zichzelf moet staan.
Continuering van het STIP deelprogramma, specifiek ontworpen vanwege de implementeerbaarheid, dient in het licht van deze evaluatie herzien te worden binnen het brede palet van het vergroten van de implementatie en implementeerbaarheid van gehonoreerde en te honoreren projecten.
Op een meer beleidsmatig niveau biedt het programma goede aanknopingspunten voor verdere aansluiting bij en versterking van kennis- en implementatieagenda's van patiëntenverenigingen, beroeps- en wetenschappelijke verenigingen zoals NHG, KNMP, FMS, het programma Zinnige Zorg van het Zorginstituut Nederland of relevante branche-brede initiatieven van verzekeraars en farmaceutische bedrijven.

[1] Ministerie van Volksgezondheid, Welzijn en Sport. Opdrachtbrief programma Goed Gebruik Geneesmiddelen (GMT/VDG/3062142), 25 mei 2011.

3.6. Output en impact

Het onderzoek van Technopolis wijst erop dat het nog te vroeg is om reële veranderingen en verbeteringen rondom het gebruik en toepassing van geneesmiddelen te kwantificeren. Wel bieden de pijplijn van 128 lopende onderzoeksprojecten en de resultaten van de 14 afgeronde projecten een breed repertoire aan nieuwe, klinisch relevante kennis die nu hun weg naar de praktijk moeten vinden. Onder deze projecten zijn er ook een aantal die een mogelijke impact op kostenbesparingen laten zien, dan wel aannemelijk maken.
De Externe Evaluatiecommissie is onder de indruk van de grote impact die het GGG-programma heeft op de kennisinfrastructuur rondom gebruik en toepassing van geneesmiddelen. Onderzoekers zoeken elkaar op, agenderen relevante vraagstellingen, ontwikkelen interacties met het zorgveld en werken aan consortia die aanvragen indienen en, bij selectie door ZonMw, uitvoeren. De jaarlijkse GGG-congressen worden goed bezocht door vele honderden onderzoekers, zorgverleners en beleidsmakers. In totaal heeft het GGG-programma sinds 2012 al in meer dan 900 publicaties in de vakpers, nationaal en internationaal, geresulteerd. Deze actieve en inspirerende mobilisering van onderzoekers en het zorgveld heeft niet alleen directe effecten op het GGG-programma, maar kent ook veel 'bijvangst' op het gebied van het bestendigen van onderzoeksconsortia, dataplatforms en registraties. In het onderzoek van Technopolis worden daar diverse voorbeelden van gegeven.
Ongeveer een kwart van de projectleiders van de afgeronde projecten lijkt vooralsnog sceptisch over de directe impact van hun onderzoek op de dagelijks praktijk. Hierboven merkte de commissie al op dat de implementeerbaarheid meer aandacht verdient.
Vergelijkbare ervaringen constateert Technopolis bij de projecten in het deelprogramma 'Registraties'. Het onderzoek van Technopolis wijst op knelpunten en uitdagingen op het gebied van de techniek van registraties, dataleemtes op transmurale grensvlakken en gebrek aan standaardisering van classificatie, codering en processen. De evaluatiecommissie vraagt zich af of ZonMw bij de toekenning van onderzoeksgelden voor registraties niet meer eisen moet stellen aan de opzet van de registraties en een meer sturende regierol moet spelen om te komen tot meer standaardisering in het veld.

4. Aanbevelingen van de Externe Evaluatiecommissie GGG

Op basis van het bovenstaande formuleert de commissie de volgende aanbevelingen:

1. Meer programmatische sturing en regie op de aanvraag en selectie van de onderzoeksprojecten lijken wenselijk. Deze evaluatie wijst op het risico van fragmentatie en gebrek aan samenhang en onder-of oververtegenwoordiging van relevante onderzoeksvelden en -disciplines.
2. Daar waar inhoudelijk gewenste onderzoeksvoorstellen bij indiening methodologisch te kort schieten, wordt aanbevolen om na te gaan of ZonMw een faciliterende rol kan spelen bij het zoeken naar methodologische ondersteuning. Dit geldt in het bijzonder voor onderzoeksgebieden als 'polyfarmacie en therapietrouw'.
3. Sturing op de standaardisering van de technische aspecten, classificaties en codering bij het opzetten van registraties wordt aanbevolen.
4. Hernieuwde inspanningen in het betrekken van private partijen bij het GGG-programma zijn gewenst om het in aanleg geformuleerde *multiplier effect* te bereiken, onder andere door het ontwikkelen van sector/industriebrede *business cases*.
5. Ten behoeve van een goede implementatie van de onderzoeksresultaten dient de driehoek vraagsteller-onderzoeksveld-zorgveld versterkt te worden wat betreft vraagarticulatie, methodologie van onderzoek en implementeerbaarheid.
6. Verdere versterking van de rol van patiënten/eindgebruikers bij het GGG-programma, onder andere bij de monitoring en het faciliteren van de onderzoeksprojecten.
7. De GGG-raad heeft grote betekenis voor het GGG-programma; betere aansluiting bij (de vragen uit) het onderzoeks- en zorgveld (minder *high level*) zou deze rol nog verder kunnen versterken.
8. De evaluatie laat een enorme potentie zien wat betreft directe en indirecte opbrengsten van GGG. Het verdient aanbeveling deze tussentijds meer expliciet te maken.

5. Bijlagen

Bijlage 1: Technopolis report: Interim evaluation of the Rational Pharmacotherapy (GGG-)Programme

technopolis |group|

November 2017

Interim evaluation of the Rational Pharmacotherapy (GGG-)Programme

Final report

technopolis|group|

Interim evaluation of the Rational Pharmacotherapy (GGG-)Programme

technopolis |group| November 2017

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Background to the evaluation

In the quest to improve healthcare, new and innovative medicines garner a lot of attention, but making better use of existing medicines is just as important. This can, for instance, mean understanding better which patients benefit from a particular treatment or tackling problems with adherence to medication. This field is known as rational pharmacotherapy.

In 2010, the Netherlands Organisation for Health Research (ZonMw) prepared a report for the ministry of VWS on identified knowledge gaps in the field of rational pharmacotherapy. In response, the ministry commissioned ZonMw to set up the Rational Pharmacotherapy programme, known in Dutch as the programme 'Goed Gebruik Geneesmiddelen (GGG)'. The programme was launched in 2012 to better understand and promote rational pharmacotherapy in practice. Up to May 2017, the programme has allocated €45.5m.

In 2017, five years after the launch of the programme, ZonMw commissioned the Technopolis Group to conduct an external interim evaluation, covering 2012 until mid-2017. The purpose of this evaluation was to assess the efficiency and effectiveness of the GGG-programme. The evaluation drew upon primary and secondary programme level data, (group) interviews, a survey among project leaders, and a review of selected projects. An independent committee of experts supported the evaluation process by interpreting and contextualising findings and by formulating conclusions and recommendations. The evaluation resulted in this underlying report by Technopolis Group and a separate document by the expert committee (not included here).

Programme organisation and management

The overall mission of the GGG-programme is to ensure that existing medication is deployed in a more effective, safe and efficient manner, to enhance the quality of pharmacotherapeutic care for patients and to improve cost-efficiency in care or for society. To this end, the programme focusses on making possible **research**, strengthening the **infrastructure** and encouraging **implementation** initiatives to ensure that knowledge about the use of available drugs comes into practice faster. These focus areas of the programme have been visualised as a house with three levels. Within the research level, four further 'rooms' or thematic priorities can be identified: effectiveness & efficiency, tailored pharmacotherapy, therapy adherence & polypharmacy, and other indications. The different priorities are each addressed through projects.

The GGG-programme has a clear organisational structure that appears well-suited to the programme's objectives. Day-to-day management is performed by the programme office. The office staff is widely viewed as committed, professional, and knowledgeable. Thematic steering is provided by the GGG-council, composed of stakeholder representatives. This high-level engagement of stakeholders is considered a strong feature of the programme. The selection of projects is the responsibility of programme committees, herein aided by external reviewers and patient panels.

While the programme office and committees are well regarded, they face a substantial administrative and managerial workload, which necessitates clear priority setting. Furthermore, the role of the GGG-council in liaising between the programme and other stakeholders could be strengthened. Also, the programme is still exploring how they can improve the functioning of the patient panels.

Programme composition

Initially, projects were funded through two main modalities: the Open Round and the Registry modality. Since then, in response to specific identified challenges within the programme, several new modalities have been added. During the evaluation period, the four principal modalities by which projects were funded were:

• Open Round (2012)	The principal modality of the programme (104 projects)
• Registry (2012)	To support the development of patient registries (16 projects)
• STIP (2014)	To stimulate the implementation of research findings in practice (19 projects)
• Large Multicentre Trials (2015)	To facilitate large projects of over €1m (3 projects)

Together, projects funded by these modalities covered all thematic priorities; however, that coverage has been markedly uneven. Over a third of all projects addressed questions around efficiency & effectiveness, whereas only nine projects dealt with therapy adherence or polypharmacy. Possible explanations for this potentially sub-optimal balance have been provided, but an in-depth analysis of underlying causes was outside the scope of this evaluation. The average success rate for initial applications (project ideas) was 14%, with some variation across funding modalities. This is consistent with many other research funding programmes, both within ZonMw and elsewhere.

The addition of new modalities and fine-tuning of existing modalities demonstrates the programme's willingness to learn and shows a flexibility to respond to challenges. The complexity of the rational pharmacotherapy topic requires such responsiveness and the programme is to be lauded for it.

That flexibility, however, may come at a cost. The programme risks becoming a mix of individual modalities rather than a coherent programme if the programme structure is not given sufficient time to stabilise. Coherence is further challenged by the way projects are selected. Currently, most of the programming is left open, enabling the field to signal its priorities. This has resulted in a very diverse project portfolio. Increased synergy between projects, which allows generation of a proper base of evidence, would likely facilitate greater uptake of findings in practice.

Programme results

Since its creation, the GGG-programme has grown into an important funding source for research in the field of rational pharmacotherapy. Although many projects are still ongoing, the programme has already delivered a substantial research output. Thus far, over 900 articles have been published that have been linked to research supported by the programme. This equals an expected average output of seven publications per project.

The programme has also fostered greater collaboration within the academic community. It has managed to engage a variety of parties that have not traditionally been involved in research projects of this kind and has put rational pharmacotherapy on the agenda of a wide range of parties. However, the programme could still benefit from greater engagement with, for instance, practitioners, professional medical associations and regulatory bodies.

At the time of the evaluation, most of the research activities were still ongoing or had only recently been completed. It is therefore premature to draw firm conclusions about contributions to the overarching programme objectives. Still, results achieved to date signal that the programme has a great deal of potential to contribute to more efficient, safer and effective use of available medication. This evaluation presents numerous examples of projects that have already provided, or are likely to provide, important contributions to the efficiency and effectiveness of pharmacotherapy when put into practice. Additionally, the programme has supported a range of projects that may reduce unnecessary or ineffective medication.

At the same time, it is clear that – despite commendable efforts by the programme office and GGG-council – the implementation of results in practice remains a challenge. There is an inherent tension here between the programme's ambitious objectives, which suggest a responsibility for ensuring that research results are implemented in practice, and ZonMw's actual mandate as a research funder. The question is therefore where the responsibility for implementation should rest and what the programme can do to further stimulate this, beyond the tools it already has at its disposal.

1 Introduction

1.1 Background, aim and scope

In 2012 the ministry of Health, Welfare and Sport (VWS) commissioned the programme on 'Rational Pharmacotherapy' (known in Dutch as the programme 'Goed Gebruik Geneesmiddelen (GGG)', hereafter called the GGG-programme).

Technopolis Group was asked to conduct an interim evaluation of the GGG-programme. This report presents the results of this evaluation.

As part of the evaluation an independent committee of experts, chaired by prof. Leufkens, was established to support the evaluation process, to interpret and contextualise the evaluation findings and to formulate conclusions and recommendations (to be presented separately by the committee).

The members of the evaluation committee are listed in Appendix A. Technopolis' evaluation team met with the evaluation committee on 11 April, 16 May, 28 June, 13 September 2017.

The evaluation focussed on:

- the efficiency of the GGG-programme: the relation between inputs and effects: are the processes and the organisation of the GGG-programme designed to achieve the stated goals?
- the effectiveness of the programme: the extent to which the programme has succeeded in achieving its stated objectives. A clear distinction is made between the (immediate) outputs, results (research findings and their translation into practice), and the (longer term) impacts.

The focus areas were operationalised in a list of evaluation questions (Appendix A).

While the scope of the evaluation was the period 2012-2017, project results of earlier programmes that in 2012 were absorbed in the GGG-programme have also been taken into account.

1.2 Methodology

This evaluation is based on the use of multiple methodologies and data sources:

- Desk research was performed to better understand the structure and activities of the programme, and the roles of the different bodies involved. Important sources of information were GGG-programme texts from 2012 and 2015 (Appendix L presents the reference list).
- The composition of the project portfolio was analysed in-depth to gain insight into how funding was allocated across multiple variables, such as programme modalities, thematic priorities, medical specialties, and type of applicants.
- In early 2017, the programme office conducted a survey among project leaders of ongoing and completed projects that were funded under the GGG-programme or the programme's predecessors. An analysis of these survey responses has been incorporated into the relevant sections of this report.
- As a full analysis of the results and impacts of the entire project portfolio was not feasible within the scope of this evaluation, therefore a project level analysis was conducted on a sample of projects considered to be representative of the portfolio. This project analysis included a review of the available project documentation (full applications, progress reports and /or final reports) for 26 projects. Additionally, we conducted in-depth interviews with principal investigators of nine of the sampled projects.
- Interviews were performed with the GGG-programme coordinators and a wide range of other stakeholders. The latter group included representatives of regulatory bodies, patient organisations, (primary) care organisations, associations of medical professionals, and (potential) co-financers. The list of interviewees that contributed to this evaluation can be found in Appendix C. Input from the interviewees is used throughout the report to substantiate our findings.

- Group interviews were held with members of the programme committees and the Rational Pharmacotherapy Council (hereafter called GGG-council).
- Two interviews were held with principal investigators for projects that had unsuccessfully applied to the programme. Purpose of these interviews was to get a more rounded view of the value of the programme to researchers in terms of funding alternatives, as well as to get a different perspective on the application process itself.

The individual methodologies are further elaborated in the corresponding chapters and annexes.

1.3 Study limitations

As with any study, this evaluation knows several limitations. These can be broadly classified into limitations related to data quality, based on completeness and accuracy of analysed data, and those related to representativeness, affecting the extent to which findings can be generalised across the programme as whole.

First, our analyses of the portfolio composition and project results have been based on data provided by the programme office. Where possible, we have taken care to verify internal consistency of data within and across provided data sources. Any inaccuracies observed (e.g. due to typographic errors or inconsistencies in nomenclature) were discussed with the programme office and as much as possible resolved. Although the possibility of persistent data errors cannot be completely excluded, we estimate that the effect of this will be minimal. The data used for the portfolio analysis only span the Open Round, STIP, Registries and Large Multicentre Trials modalities. For the Personalised Medicine and Rediscovery modalities no data were available yet as these modalities had just started.

Furthermore, some of the categorisations used throughout this evaluation were not developed *a priori* and were therefore assigned retrospectively by the ZonMw programme office with input of the external evaluation commission. This, and additional decisions made by the evaluators on categories, classifications of organisations and specialisations are further detailed in a full methodological note that can be found in Appendix J. Analytically, projects could not be assigned more than one label per category (e.g. per thematic priority, or target population) even when multiple labels would have been appropriate. In such cases, only the label considered most relevant was assigned. Consequently, there is a degree of underrepresentation in certain categories, although the overall effect of this is comparatively small.

Also, the analysis of the programme efficiency was restricted to the relation between project inputs (i.e. the funding allocated to projects) and outputs and outcomes thereof and, at a higher level of aggregation, realised and expected impacts of the programme. Efficiency of the programme management could not be analysed, as the evaluators did not possess data on resources invested to operate the programme office, nor on how this would compare to other (ZonMw) programmes. This aspect was considered outside the scope of the present evaluation.

Multiple factors, derived from the chosen methodologies, influence the extent to which our analyses can be considered representative of the programme of the project portfolio. The first factor relates to the analysis based on stakeholder interviews. In any evaluation of this kind, but particularly with a programme the size and scope of the GGG-programme, it is not feasible to interview all (potential) stakeholders. Therefore, a selection was made of interviewees who were deemed to have sufficient knowledge of the programme to meaningfully discuss aspects thereof or who represented important stakeholder groups. The selection was done in careful consultation with the client and the independent evaluation committee. Although this selection process helped to ensure balance of viewpoints, it also entailed substantial heterogeneity among interviewees, both in terms of their relation to the programme and of the type of relevant knowledge they possessed. Consequently, certain issues were discussed in only a small number of interviews. Furthermore, by its very nature, interview data tend to include more subjective opinions. Such opinions are valuable not only because they capture aspects of the programme that are not readily covered by other data sources, but also because they provide insight into where perceptions differ from more objective realities. Where possible, we have triangulated interview data with other data sources to determine whether opinions could be substantiated. However, such triangulation was not possible in all cases. Where the evaluators felt that otherwise unsubstantiated

opinions, even those expressed by individual interviewees only, provided important context, we have chosen to include this in the analysis but have clearly indicated this. Such opinions should therefore be interpreted as potential areas for further investigation, rather than as the basis for drawing conclusions and recommendations.

An additional limitation on the degree to which our findings can be generalised across the project portfolio rests in the project level analysis. As, within the constraints of this evaluation, it was not possible to review the entire project portfolio in detail, we selected 27 projects for in-depth analysis. At the time of analysis, final project reports were available for 11 of these. The remainder were either still ongoing or had been terminated. In the here presented analysis, the main focus is on outputs and outcomes of projects as, in most cases, insufficient time has passed between completion of the projects and the time needed for impacts to materialise in practice.

1.4 Structure of the report

The subsequent sections of this report are structured as follows: Chapters 2 through 4 are primarily centred on *process* dimensions of the evaluation. Chapter 2 outlines the history and objectives of the programme and introduces the actors directly involved with the programme. Chapter 3 reviews how the programme has been structured to enable the translation of strategic goals into specific activities. Chapter 4 analyses how the project portfolio has been composed along various dimensions.

Having discussed the process dimensions, Chapter 4 focuses on the *results and impacts* generated through the projects funded by the programme. Last, Chapter 6 summarises the main findings and conclusions of the evaluation.

2 Organisation of the programme

2.1 Background

The GGG-programme was launched in 2012 after a preparatory phase that started in 2009 when the ZonMw-report 'Signalement Goed Gebruik van Geneesmiddelen' was offered to the Dutch Parliament. In this report, experts stated that there were gaps in the rational use of medication that could have consequences for the effectiveness of care (ZonMw, 2012). Identified knowledge gaps were:

- Is medication prescribed when needed?
- Is the right medication prescribed, in the right dosage?
- Are medicines used for other effective indications when possible?
- Is medication used correctly?

In response to the report, the ministry of VWS asked ZonMw to further investigate these gaps. The report 'Verdieping Goed Gebruik Geneesmiddelen' was offered to Parliament in 2010 (ZonMw, 2010). It showed:

- Too little research on existing drugs on a wide variety of topics
- Fragmentation in the existing infrastructure for drug research with existing drugs
- Lagging implementation of the gained knowledge (in guidelines and in practice)
- Unreliable, temporary and fragmented funding opportunities

Based on the conclusions of the second report, the ministry of VWS tasked ZonMw to set-up the GGG-programme: a structural programme that focused on gaps in rational use of medication that were not picked up in the existing system, both in extramural and intramural care (ZonMw, 2012). According to the ministry of VWS the programme should aim to improve the quality of care, the efficient use of medication and to ensure that fewer hands are needed to provide care (Huijts, 2012).

Several ZonMw programmes that were started before 2012 were put under the umbrella of the GGG-programme. These are: Priority Medicines for Children (PMK), Priority Medicines for Elderly (PMO), Expensive and orphan medication (IEMO), Efficiency research (pharmacotherapy part) (Doelmatigheidsonderzoek, DO) and the modality priority medicines antimicrobial resistance (optimisation of antibiotics therapy: dosage and use).

In June 2015, it was decided that the programme would be extended until 2019 (ZonMw, 2015) (Schippers E. I., 2016).

2.2 Mission and goals

The overall mission of the GGG-programme is to ensure that (existing) medication is deployed in a more effective, safe and efficient manner, to enhance the quality of pharmacotherapeutic care for patients and to improve cost-efficiency in care and/or for society (ZonMw, 2012). To contribute to the mission of the programme, eight **strategic goals** were formulated (Table 1).

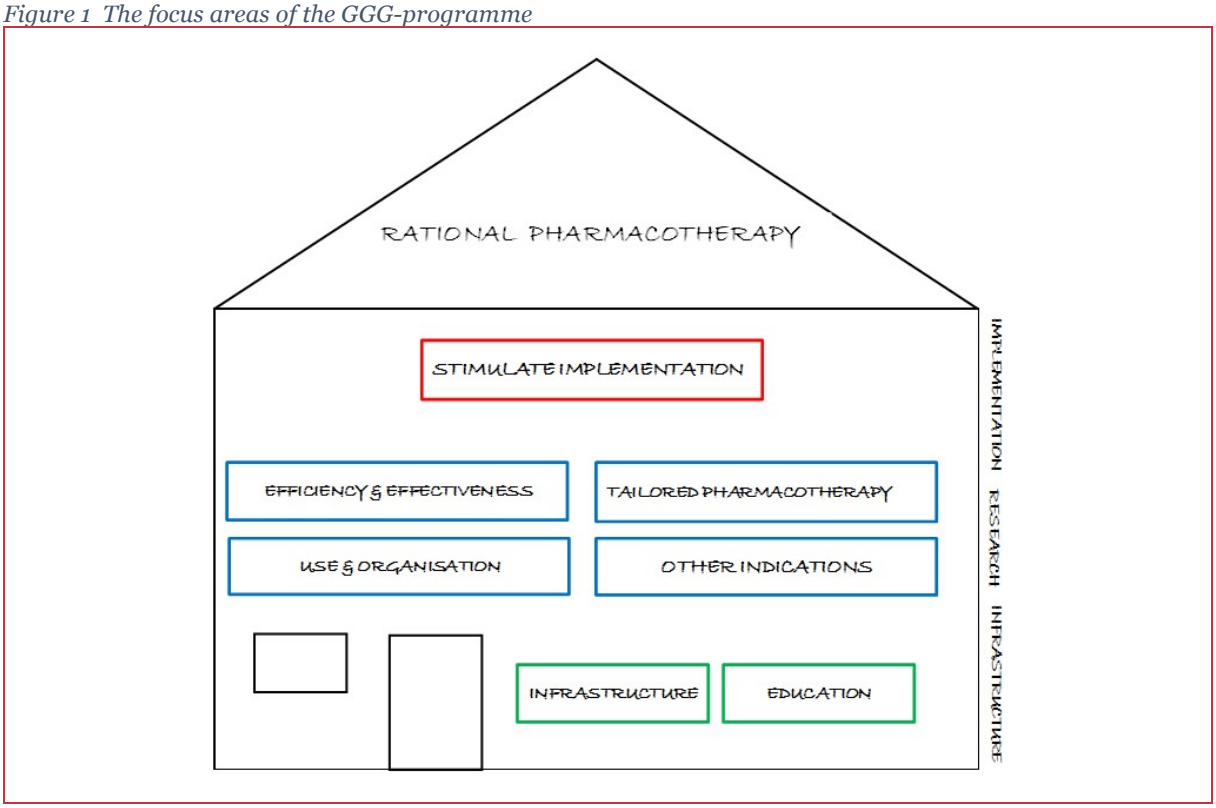
Table 1 Strategic goals of the GGG-programme

1. Facilitate pharmacotherapy-related research to provide evidence to substantiate the 'pharmaceutical care' sections of guidelines and/or care standards.
2. Answering pharmacotherapy related research questions that result in the improvement of quality of care in practice, where there is a need
3. Address pharmacotherapy-related research questions that are relevant to the work of decision-making bodies, including the Medicines Evaluation Board (in Dutch: CBG) and the National Health Care Institute (in Dutch: ZiN)
4. Identifying and conveying solutions to possible bottlenecks in the implementation of (available) pharmacotherapy related knowledge in guidelines and/or care standards, in practice and in decision making
5. Strengthening the infrastructure in which relevant questions around rational pharmacotherapy can be answered in the right way (both observational research and intervention research)
6. Building and maintaining a network of parties that are involved with pharmacotherapeutic care and rational pharmacotherapy, specifically in the development of guidelines and care standards, registrations, decision making, knowledge transfer, implementation and research funding.
7. Staying up-to-date with relevant developments around rational pharmacotherapy and finding connections where necessary
8. Developing into a structural source of funding of research in rational pharmacotherapy in the Netherlands

Translation of Programme Document, ZonMw (2012)

To achieve these goals, the programme focusses on making research possible, strengthening the infrastructure and encouraging initiatives to ensure that knowledge about the use of available drugs comes into practice faster and is actually used. These three main focus areas of the programme are visualised by ZonMw as a house with three levels and several 'rooms' (hereafter referred to as 'thematic priorities') (Figure 1). Each of these three focus areas broadly aligns with one of these levels. The **research** made possible by the programme has been categorised into four thematic priorities, namely: efficiency & effectiveness, tailored pharmacotherapy, other indications, and use & organisation. Collectively these form the central level of the house. Underpinning this is the **infrastructure** that forms the bottom level of the house. The thematic priorities within this have been divided into activities aimed directly at developing the research infrastructure (such as patient registries) and educational activities to increase understanding of rational pharmacotherapy. The linkage between the research and its uptake into practice is formed by activities to stimulate **implementation**, visualised by the top level of the house.

Figure 1 The focus areas of the GGG-programme

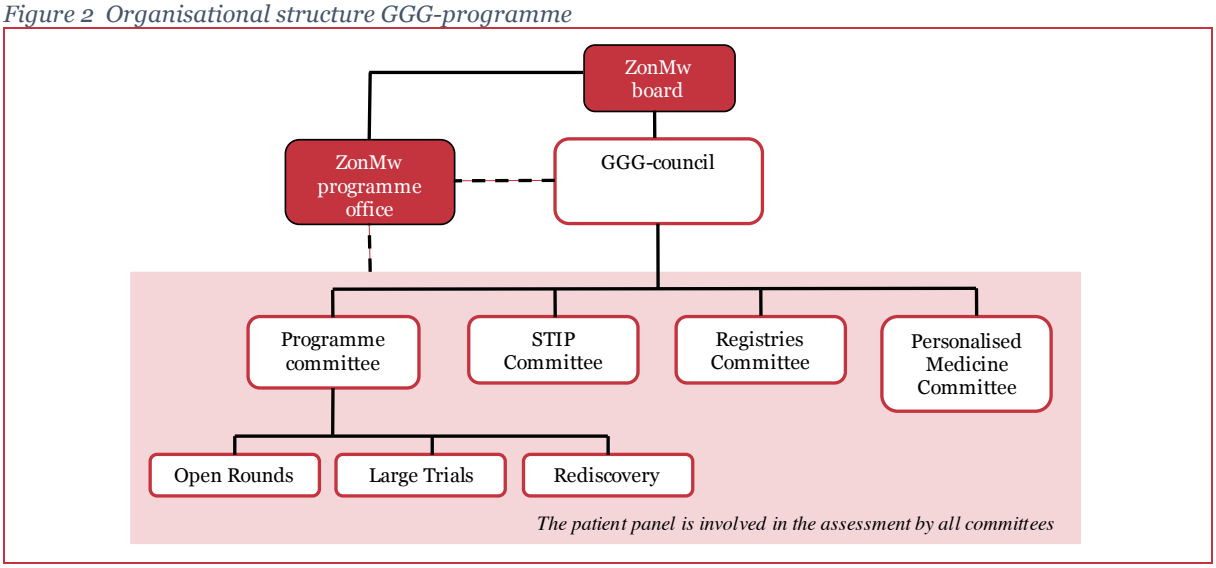


ZonMw (2014)

2.3 Governance structure

Several bodies are involved in the organisation and implementation of the programme: the ZonMw board, GGG-council, ZonMw programme office, programme committees and the patient panels. The role of these bodies and their contribution to the programme are described in the following sections.

Figure 2 Organisational structure GGG-programme



Source: Technopolis Group based on programme text GGG-programme (2015) and interviews

2.3.1 ZonMw board

The board of ZonMw is officially responsible for the implementation and coordination of the programme as it has the managerial and regulatory final responsibility for the programme. The board of ZonMw periodically accounts to its commissioning party, the ministry of VWS (ZonMw, 2012). In practice, the work is delegated to the GGG-programme office and the responsible board and committees. However, the board remains the official body through which strategic and delicate decisions regarding the GGG-programmes are made. They should, for example, approve any financial partnerships with third parties at programme level, approve the programme's annual report, appoint members of the GGG-council and approve the funding decision of GGG-programme committees (ZonMw, 2015).

2.3.2 GGG-council

The GGG-council was established within the GGG-programme with the specific aim to steer the programme thematically to ensure that the GGG-programme fulfils its societal importance, namely by optimising the use of medication, the quality of care and the efficient use of available medication (ZonMw, 2015). The council's focus is on the overall goals of the GGG-programme and it formulates preferred themes and focus areas for investments and contributes to the creation of societal support for the GGG-programme. The council is responsible for the allocation of budget among the different modalities and decides whether a sub-programme with financing from an external party such as pharmaceutical companies, health insurance companies or health charities can be added to the GGG-programme. Furthermore, the council provides input for the programme's annual plan describing the planned activities, results, the corresponding budget and the allocation of the project budget among the different modalities. Finally, the council can stimulate new initiatives and plays a role in discussing implementation of the results of the programmes projects. Potential hurdles for implementation of the results of individual projects are addressed and discussed in the council meeting.

The members of the council are appointed for four years and nominated by stakeholder organisations (representing organisations of patients, medical specialists, nurses, pharmacists, the pharmaceutical industry, general practitioners, etc.), though they act without obligation or compulsion. The council is led by an independent chairman, appointed by the board of ZonMw. The chairs of the programme committees are also members of the GGG-council to ensure that the activities of the committees and the GGG-council are aligned. The ministry of VWS and the chair of the ZonMw board are allowed to be present during meetings as observers. The council meets at least two times a year to discuss suggestions for the content of the programme, as well as new developments and possible bottlenecks (ZonMw, 2012). The council is not involved in the selection process itself but is informed of the outcome of the calls.

The fact that a council of stakeholder organisations has been given important steering power is rather unique for ZonMw. Although the council has no decision-making power regarding the selection of projects (which lies with the programme committees), it decides on the allocation of approximately €10m to €11m annually among the different modalities. The council's focus is on the overall goals of the GGG-programme and it formulates preferred themes and focus areas for calls that take place within the modalities. An example is the STIP call, where the council advised to prioritise proposals from smaller, non-research projects addressing implementation of existing knowledge (ZonMw, 2015). Overall, within the council a bottom-up approach to programming is favoured, because researchers are considered to be best placed to determine the needs of the field and translate these into research proposals.

There were also committee members who expressed their frustration that a project that was felt to be of high relevance, with the potential for significant impact, could not be granted because the scientific quality was not considered sufficient. Members of the GGG-council also expressed their wish to use part of the GGG-budget in a more flexible manner so they could fund projects that do not fulfil the regular criteria, but that are expected to deliver a large impact on the effective, safe and efficient use of medicine. Under the current programme structure this is not possible.

The council meets only twice a year and members are sometimes only peripherally involved in rational pharmacotherapy in their daily professions. For the council to function optimally it is important that each member is sufficiently informed and empowered to contribute to the discussion. Interviews with

GGG-council members suggest that sometimes it takes time for new members of the council to fully understand the nature of the programme, which may hinder their ability to meaningfully contribute in this period. Some people closely familiar with the programme and the GGG-council have indicated that, in their opinion, the role of the council could be further strengthened, although no specific suggestions were offered as to how this should be done.

2.3.3 Programme committees

The GGG-programme consists of several funding modalities. For each modality, a programme committee has been installed to steer its content. The main tasks of these programme committees are:

- Executing the modality according to the approved programme proposal and the annual plans. Meanwhile, the target of the programme, the unity and the coherence within the programme should be monitored
- Setting up calls for proposals that can contribute to the goals of the modality
- Assessing the proposals on the different criteria conform the goals of the modality
- Prioritising the proposals based on the proposal text, reviewer comments and rebuttal of the applicant, and presenting these to the ZonMw board for approval
- Approving the composition of potential supervisory committees of the accepted projects
- Signalling developments that are of importance to the programme, and when necessary giving advice to the ZonMw board and the GGG-council
- Safeguarding the progress and evaluation of the accepted projects based on the progress report that each project should deliver halfway through the project and the final report at the end of the project
- Safeguarding the progress of the (sub)programme and informing the GGG-council and the ZonMw board about this

The ministry of VWS and - if applicable - third parties that contributed to the programme can be present during meetings as observers. The members of the committees are appointed for a set period. The chairmen of the committees are also seated in the GGG-council. (ZonMw, 2015)

The committees' main responsibilities lie in the selection of the projects, which is an essential role in the GGG-programme. The committees are carefully composed, taking into account the diversity of expertise needed to assess proposals on the selection criteria. Depending on the specificities of the calls for proposal, the composition of the responsible programme committee can vary per call. The composition is further influenced by the need to avoid potential conflicts of interest, as laid down in the ZonMw code on Conflicts of Interest (ZonMw, Gedragscode Belangenverstrengeling ZonMw, 2010). Initially, the programme functioned 'in the spirit' of the code, meaning that committee members with a potential conflict of interest could not be present during parts of a meeting when the projects in which they had a potential interest were discussed. Following a granted appeal, and a ruling by the ZonMw Appeals Commission, currently a stricter interpretation is followed. This means that committee members with a potential conflict of interest are excluded from the assessment procedure altogether. Consequently, the initial pool of committee members required significant expansion.

Although, in theory, the tasks related to monitoring and evaluation of projects are delegated to the programme committees, in practice a substantial part of this work is done by the programme office to reduce the workload of the committees. Overall, interviewees with good knowledge of the responsibilities and activities of the committees appear mostly satisfied with their functioning. Nonetheless, several areas were flagged for improvement.

- Committee members experience their workload as high. Some indicate that this could be improved if ZonMw would take over some of the (sub)tasks in the process, or if the assessment templates used would be simplified. Some interviewees complained about the need to repeat themselves in the template. Others would like to simplify the assessment criteria: "*in the end all that matters are the criteria 'relevance' and 'quality'*".

- Interviewees express a desire for more information from the programme office. Some wish to get intermediate (e-mail) updates on the modality they are involved with, while others would appreciate receiving more information on the developments within the programme overall.
- There is a feeling with the programme committees that, because there are so many projects funded by ZonMw as a whole, it is almost impossible to know if there is duplication of activities. The committee members are mostly unaware of projects outside their modality, let alone outside the programme, and express concern whether there is sufficient overview at ZonMw of all other funded projects. The programme office itself indicates that there is regular contact with other relevant ZonMw-programmes to avoid duplication.
- Similar to the previous point, some committee members feel that they do not have sufficient overview of proposals discussed in other GGG-modalities to ensure coherence within the programme. Although the chairs of the committees are represented in the GGG-council and would have access to this information, it appears that this knowledge is not always shared within the committees.
- Some committee members indicate they would welcome more contact with referees from the patient panel. Now, they only receive written assessments by the panel, while sometimes more information is desired about why a patient panel assesses a project as relevant.
- Although it is widely understood why the programme has moved towards a stricter compliance with the code on conflicts of interest, some committee members and the programme office have indicated the current system presents a challenge to recruiting a sufficiently large number of people with relevant expertise that can serve as independent committee members.
- Interviewees indicated that, although the committees are carefully composed, currently they lack presence of people with practical knowledge on how to implement innovations.

The evaluators' impression is that most of these issues have already been raised by the committee members to the programme office. This indicates that there is an open and constructive relation between these bodies. In some cases, actions have already been taken by the programme office to find a solution. To illustrate, during the evaluation period a meet-and-greet has been organised between the patient panel and the programme committee to discuss mutual expectations and improve the collaboration.

2.3.4 ZonMw programme office

The ZonMw programme office oversees the daily implementation of the GGG-programme. The office consists of two programme coordinators, programme officers and programme assistants. They are supported by administrative staff and a communication and implementation staff member. In total 17 ZonMw staff members (12 FTE) are affiliated with the programme office.

Specific tasks of the programme office are (ZonMw, 2015):

- Coordinating the daily execution of the programme according to the approved annual plan
- Coordinating all programme- and other operations to support the GGG-council and the programme committees
- Taking care of the communication and implementation of the programme
- Maintaining the contacts with the project leaders of financed projects, as a delegated task of the programme committees
- Keeping the programme committees and the GGG-council informed about relevant developments that could be of influence on the GGG-programme and proposing specific changes when considered necessary
- Shaping a GGG-specific network in which the exchange of relevant (international) developments with and between parties is possible

Members of the programme committees and the GGG-council indicated that they are very satisfied with the role and functioning of the programme office and feel well supported. Questions or issues that are raised by committee members are addressed in a quick and efficient manner by ZonMw's staff.

ZonMw's staff members are described as committed, pro-active, professional, knowledgeable and pleasant to work with. This sentiment is shared by interviewed project leaders of funded projects. At the same time, the programme office indicates that it has insufficient resources to realise all of its ambitions. There is, for example, insufficient capacity to specifically focus on implementation. The programme office considers the monitoring of projects and the analysis of end reports to be very time consuming. Potential end users, such as the medical professional associations and regulatory bodies, indicate that they would appreciate a proactive role of the programme office in communicating the results of projects to relevant organisations. A 'heads up' on the (potential) outcomes of projects before the actual scientific results are published could save a lot of time in, for instance, the revision of (modules of) clinical guidelines. While it is very likely that the programme office is aware of these specific opportunities for improvement, they are limited by the capacity available.

2.3.5 Patient panels

Since 2014, a patient panel takes part in the assessment process of proposals submitted within the GGG-programme. The panel assessing proposals in the Open Round and STIP modalities is coordinated and trained by the Patient Federation Netherlands[1]. This patient panel gives its perspective on the relevance and feasibility of projects (both project ideas as full project proposals) and assesses how well patient participation is included in the research. The different panel members are invited to register for the assessment of a certain call, and assess the proposal on the criteria mentioned above. They score and comment on the proposals which is then discussed during a work session with other panel members. Their advice is sent to the Patient Federation Netherlands, which does the final check and submits the assessment to ZonMw. The assessment is used by the programme committee during the selection of proposals.

In 2016 an evaluation took place that looked at the effect of patient panel involvement on reaching the programme's goals (APE Public Economics, 2016). It concluded that there was only a limited effect and formulated a number of recommendations. A reason for the limited effect, according to APE Public Economics, was that the evaluation focussed on granted projects from the first subsidy rounds. During this start-up phase, there was still a lot of variation in panel review quality and panellists were less experienced. According to a person with close knowledge of the patient panel, this has improved since then. This person also reported that there is an increased exchange between the panel and the programme committees[2]. However, this person feels that is it important that patients are involved in every step of the programme cycle, including monitoring and evaluation of the projects, which is currently is not sufficient according to his/her opinion.

Consequently, the programme office and ZonMw are trying to further optimise the process and to strengthen the position of the patient in the process.

[1] The panel assessing the proposals in the Personalised Medicine modality is coordinated by the Dutch Cancer Society.

[2] Recently a meet-and-greet has been organised between the patient panel and a programme committee to discuss mutual expectations and improve the collaboration (as mentioned in section 2.3.3). Assessment committees (e.g. modality Personalised Medicines) include patient representative and the director of the Patient Federation Netherlands is a member of the GGG-council.

3 Programme structure

As discussed in the preceding chapter the GGG programme has been designed as a house with several 'rooms' (the thematic priorities). To 'furnish' these rooms, the programme has developed various funding modalities and activities. Some of these were conceived at the onset of the programme, whereas others have been added over time. In this chapter, we begin by introducing the different funding modalities and describe the evolution of the programme over time. In the subsequent sections the modalities and other activities have been reviewed against the focus areas and thematic priorities of the programme.

3.1 Programme evolution

The different modalities developed within the GGG-programme are presented in Table 2, which shows the goals and the number of calls for proposals per modality.

Table 2 Module, goals and number of calls per year

Module	Goal	2012	2013	2014	2015	2016	2017
Open Round	Research: generating evidence that is usable in practice	1	2	1	1	1	1
Registries	Infrastructure: making data from daily practice available	1	1	1	1		
STIP	Practice improvement projects			1	1	1	
Large Multicentre Trials	Research: results immediately part of practice				1	1	
Personalised Medicine	Research and implementation: treating patients based on unique characteristics				2	1	2
Rediscovery	Research: using potential of old drugs with new indications					1	1

ZonMw (2017). Not included is the topdown call (described in section 0)

At the start of the programme, in 2012, there were only two funding modalities: the Open Round and the Registries. Whereas the Open Round provides funding for research projects, the Registries modality has focused on infrastructure development in the form of patient registries (ZonMw, 2012).

In 2014, the Stimulation Application In Practice (STIP) modality was introduced to involve more primary care practitioners and to increase implementation of programme results in practice.

In 2015 the Large Multicentre Trials modality was added to the programme. Through this modality the ministry of VWS made additional budget available for large clinical studies that should provide high quality answers to questions regarding the efficient application of drugs in practice (simple large scale pragmatic trials providing answers at the highest level of evidence). Additionally, in 2015 a first call in the modality Personalised Medicine took place. This modality was launched because stakeholders (amongst which insurance company Zilveren Kruis Achmea) initiated collaborations and combined funding to address challenges with implementation of personalised medicine in Dutch healthcare. The GGG-programme was considered the right structure to host this modality.

Most recently, in 2016, a separate call was started for Rediscovery projects (ZonMw, 2016). Rediscovery concerns research regarding the effectiveness of and/or optimisation of dosing regimens for a promising application of an existing medication (unpatented or no longer patented) with an indication for which the drug is not (yet) registered (ZonMw, 2015). This involves clinical studies that further investigate potential findings from case studies and/or experimental observations. Recognising the potential value of this type of research, the GGG council decided to further stimulate more translational work in this

area without the requirement of direct implementation in daily practice. This called for a separate modality with distinct requirements.

3.2 Research

The GGG-programme is foremost a research funding programme. Therefore, most of the previously described modalities were developed to support activities in the focus area of 'research'. This section further details how the Open Round, Large Multicentre Trials, Personalised Medicine and Rediscovery modalities have been arranged. Additionally, the 'VWS Topdown projects' are introduced. Whilst projects in the STIP and Registries modalities could also be considered a form of research, they are more closely aligned with the strategic focus areas of implementation and infrastructure respectively, and are thus discussed in sections 3.3 and 3.4.

3.2.1 Open Round

The Open Round forms the core of the programme. The Open Round essentially corresponds to the programme's strategic goals of facilitating pharmacotherapy-related research to further the evidence underpinning guidelines and care standards, and thereby contributing to improvement of care. In the Open Round, researchers – in collaboration with other relevant actors (such as health care practitioners, members of professional associations or regulatory bodies, or patient organisations) – can submit a proposal for a relevant problem or question (Smid, 2016). No restrictions are put on the duration of research and the size of the requested subsidy, apart from the fact funding requests should be realistic and well-substantiated. Since 2013 around €6m has been made available each year.

The Open Round is characterised by a bottom-up approach to problem identification and is not bound to specific themes or disease areas. The underlying premise is that, through the submission of proposals, the field should signal which questions related to rational pharmacotherapy it considers relevant.

Table 3 Overview of calls per year in the Open Round modality

	2012	**2013**	**2014**	**2015**	**2016**	**2017**
Number of calls	1	2	1	1	1	1
Awarded budget	€ 9m	1. € 7.6m 2. € 5.7m	€ 6.9m	€ 5.8m	€ 6.0m*	€ 6.0m*

ZonMw (2017); *available budget, call not awarded yet (as of May 2017)

3.2.2 Large Multicentre Trials

Through the Large Multicentre Trials modality the ministry of VWS has made additional budget available for large studies that should provide high quality answers to questions regarding the efficient application of drugs in practice. Results should be directly implementable at a national level (Smid, 2016). The grant is conditional to broad support from (a) professional group(s) for tackling the identified problem. Preferably, the questions addressed should be part of the knowledge agenda of the relevant professional group or of agreements made between the ministry of VWS and the medical professional associations (ZonMw, 2016). The Large Multicentre Trials modality was introduced to facilitate projects of over €1m and has room for around three projects per call.

Table 4 Overview of calls per year in the Large Multicentre Trials modality

	2012	2013	2014	2015	2016	2017
Number of calls				1	1	
Awarded budget				€ 4.2m*[3]	€ 6.3 m**	

ZonMw (2017); * including a compensation for project ideas with a positive recommendation to help cover the costs incurred for preparing a full proposal; ** available budget, call not awarded yet (May 2017)

3.2.3 Personalised Medicine

Aim of the Personalised Medicine modality is to ensure the effective implementation of personalised medicine in Dutch healthcare by, among others, stimulating cooperation and studying the cost-effectiveness of diagnostics and treatment (ZonMw, 2015). Results should demonstrate the added value to the patient and provide evidence that enables the National Health Care Institute to advise on changes to the basic health insurance package.

The first call was the result of a collaboration between ZonMw, the Dutch Cancer Society (KWF) and health insurer Zilveren Kruis Achmea. It focussed on oncology and rare diseases. Additional criteria were that oncology projects should foremost be (cost)effectiveness studies and that projects around rare diseases should aim to provide further insights into the early diagnostics and to allow for early intervention (ZonMw, 2015; Smid, 2016). The second call, in 2016, was the result of a collaboration between ZonMw, the Dutch Arthritis Association and the Canadian Institutes of Health Research (CIHR) and focussed on rheumatism.

Two calls were launched in 2017: one call focussed on establishing an ethical and legal service desk that provides researchers with answers related to ethical and legal issues that they come across in the daily practice of personalised medicine research. The other call focussed on the development of predictive diagnostic tools in order to achieve a more efficient and targeted use of existing expensive drugs.

Table 5 Overview of calls per year in the Personalised Medicine modality

	2012	2013	2014	2015	2016	2017
Number of calls				1. Oncology 2. Rare diseases	1. Rheumatism	1. Service desk ethics and law 2. Diagnostics 3. Ethics and law
Awarded budget				1. € 2.7m 2. € 1.1m	€ 2.1m	1. € 0.1m* 2. € 9.5m* 3. € 0.5m*

ZonMw (2017); * available budget, call not awarded yet (May 2017)

3.2.4 Rediscovery

The aim of the Rediscovery modality is to stimulate projects focused on research regarding the effectiveness and/or optimisation of doses for a promising application of an existing medication (unpatented or no longer patented), with an indication for which the drug is not (yet) registered. Important is that existing pilot data and a reasonable operating mechanism are the basis of the proposed research (ZonMw, 2016). Studies should provide answers to questions regarding the efficiency of drugs in practice. Study results should eventually be implementable at a national level and at a socially acceptable price (Smid, 2016).

[3] An additional €1.4m has been awarded after May 2017, and is therefore not yet incorporated into the data provided to the evaluators.

Table 6 Overview of calls per year in the Rediscovery modality

	2012	2013	2014	2015	2016	2017
Number of calls					1	1
Awarded budget					€ 1.0m *	€ 1.0m*

ZonMw (2017) * available budget, call not awarded yet (May 2017)

3.2.5 VWS top down projects

When the ministry of VWS tasked ZonMw to set up the GGG-programme, it was agreed to reserve 10% of the programme budget for urgent policy-related projects (Huijts, 2012). For these projects the ministry of VWS decides on the most urgent policy-related questions (with input from the National Health Care Institute or the Medicines Evaluation Board (CBG)). ZonMw then issues a separate project call outside of the other funding modalities.

So far, the following six 'VWS-top down' projects have been financed:

- 2012: establishment of the Dutch Melanoma Treatment Register (DMTR) to collect data on the results of treatment of patients with metastatic melanoma
- 2013: project on the localisation of new anticoagulants
- 2015: financing of one GGG-stipendium for the best application of the online course Clinical Development Online at Paul Janssen Futurelab Leiden (see also section 3.4.2).
- 2016: a study on the effect of switching from Thyrax Duotab to other brands of levothyroxine after a stock-out of Thyrax Duotab in the Netherlands
- 2016: implementation of a Multiple Sclerosis (MS) registration of the use of immune-modulating MS agents with the ability to obtain input from patients through questionnaires and to connect them to the delivered care
- 2016: establishment of a national system to monitor the safety of biological drugs

3.3 Implementation

One of the hallmarks of the GGG programme has been its emphasis on implementation of research findings into practice. Whilst the eventual responsibility for implementation rests with the researchers and stakeholders from the field, rather than with ZonMw, the programme aims to facilitate the implementation process in various ways.

First, already in the selection of projects, feasibility of implementation is an important criterion. Furthermore, in its monitoring of project progress, the responsible programme committees and the programme office continue to emphasise implementation with the researchers involved. Where appropriate, the programme committees can also recommend the involvement of additional parties that can help drive implementation. Completed projects are discussed with dedicated communication and implementation staff from ZonMw. (Council, 2013) These staff members can in principle help researchers in the development of their implementation activities. (ZonMw, Implementatiebeleid, 2017) Last, the programme has two further instruments at its disposal that are specifically aimed at stimulating implementation. The foremost of these is the STIP modality. Additionally, ZonMw can provide so-called VIMP subsidies. These two instruments are discussed in the remainder of this section.

3.3.1 STIP

One of the strategic goals of the GGG programme is to '*idenfity and convey solutions to possible bottlenecks in the implementation of (available) pharmacotherapy related knowledge in guidelines and/or care standards, in practice and in decision making*'. The GGG council decided to add the STIP modality to the programme in recognition of the fact that the then existing modalities appeared to be insufficiently equipped to accomplish this goal. The aim of the STIP modality is therefore to bridge the gap between the generation of evidence through research and the actual implementation and uptake of

this evidence in the 'field' (ZonMw, 2015). It is focused on stimulating non-research projects by non-academic groups. STIP projects should be practice oriented, with a relevant question or broadly recognised issue from practice at its core.

Eligible for funding are (ZonMw, 2016):

- Projects that focus on the implementation of guidelines and research recommendations in daily practice.
- Practice improvement projects that can be scaled up.
- Projects that aim to improve the organisation and/or quality of pharmacotherapeutic care.

The applicant should be a person or organisation from the field. This can include parties that work in healthcare or that closely collaborate with the field and have experience with the implementation of practice projects.

In general, STIP projects are short-term (around 1 year) and can be executed with limited budget (ZonMw, 2015). During the first year there was €1.2m available, sufficient to fund eight to ten projects. The third round focussed on larger projects directed towards pilot implementation.

Since 2014 there have been three calls. Priorities are set for each funding round. For instance, the third call prioritised projects aimed at pharmacotherapeutic care for vulnerable groups, step-down/start-stop strategies for drugs, and/or shared decision making. The programme office has indicated that, over time and as a result of further discussions within the GGG-council and the STIP-committee, the call texts for the STIP modality have increasingly focused on addressing issues in areas where there is high consumption of (primary) care.

Table 7 Overview of calls per year in the STIP modality

	2012	2013	2014	2015	2016	2017
Number of calls			1	1	1	
Awarded budget			€ 1.2m	€ 0.9m	€ 1.0m*	

ZonMw (2017) * available budget, call not awarded yet (May 2017)

3.3.2 VIMP

In the final report of a project, project leaders can describe their further dissemination and implementation plans for their project results. This may lead to an invitation to submit a grant application for the Dissemination and Implementation Impulse (VIMP) of ZonMw. This grant can be up to €50k and aims to support project leaders in the dissemination and implementation of their project results. No VIMP's have been awarded within the GGG-programme as the granted projects have not reached this phase yet.

3.4 Infrastructure

The foundation of the 'GGG house' is formed by activities that are aimed at achieving the strategic goals of '*strengthening the infrastructure in which relevant questions around rational pharmacotherapy can be answered in the right way*' and '*Building and maintaining a network of parties that are involved with pharmacotherapeutic care and rational pharmacotherapy'*. Hereto, the programme supports two main types of activities. Within the Registries modality the development of patient registries is stimulated, as discussed shortly. Additionally, the programme supports a limited number of educational activities.

3.4.1 Registries

The Registries modality is intended to fund the initial phase of patient registrations that ultimately enable the acquisition of mirror information, monitoring of drug use, scientific research and reimbursement decisions.

To collect data from clinical practice a solid infrastructure is needed that should fulfil strict conditions. For this, a list of conditions and a checklist were prepared based on the report by NIVEL, RIVM, DANS and Mondriaan in 2012 (Grootveld, et al., 2012; ZonMw, 2013).

To maximise use of existing knowledge and experience available for the development and management of the data collection, facilities are made available to support the applicant with development. Close collaboration takes place with the ZonMw programme *Access to Data* (in Dutch: *Toegang tot Data*).

Table 8 Overview of calls per year in the Registries modality

	2012	2013	2014	2015	2016	2017
Number of calls	1	1	1	1		
Awarded budget	€ 0.9m	€ 1.2m	€ 1.0m	€ 1.1m		

ZonMw (2017)

3.4.2 Education

Whilst supporting research is the main goal of the programme, and has been the primary focus of this evaluation, the programme has also provided funding for several educational acitivites. Specifically, these are:

- The GGG-programme stimulates the development of Clinical Trial Applications from academic researchers by alliance with Paul Janssen Futurelab Leiden. Entrepreneurial physician-investigators and biomedical researchers in the Netherlands who wish to further their career and increase their knowledge on the development of novel and/or existing medical interventions are trained at Futurelab. In the on-campus extended part of the Clinical Development module of Futurelab, participants are mentored by clinical trial experts to develop their own clinical trial applications based on their own idea and brief pre-proposal submitted with their application. To further stimulate academic training and development in this area, the best proposal by an applicant from a Dutch research institute that encompasses research on a registered drug will receive a nomination letter from Futurelab. This proposal is subsequently assessed by the GGG committee and awarded up to € 0.5m if the quality and relevance of the proposal is sufficient.
- The GGG's programme office played a role in the initiation of a basic, national pharmacotherapy exam for novel medical doctors. This exam tests whether a doctor has sufficient knowledge to independently prescribe medicine, including knowledge about most frequent prescription errors.

4 Portfolio composition

The following chapter presents an analysis of the selection of projects and allocation of funding within the different modalities, in terms of thematic priority, area of specialty, and target group.[4] Purpose of this analysis was to gain insight into process dimensions such as generation and allocation of inputs, and accessibility of the programme.

4.1 Funding composition

At the onset of the programme, it was the intention that the funding provided by the ministry of VWS would be supplemented with contributions from other parties, such as health insurers, health foundations or the private sector (e.g. pharmaceutical companies). To better understand whether the programme has indeed been able to attract such funding, the composition of (project) funding by funding source was reviewed across the project portfolio.

In each modality, the share of ZonMw funding is at least six times that of the own contribution, which makes up the second largest source of funding (Figure 3). Industry has contributed to projects in the Open Round, the Registries and STIP modalities. At the project level, the contribution from insurance companies is minimal.

In addition to these project level contributions, there have been several financial contributions from third parties at the programme or modality level (Table 9). Most of these have come from charitable foundations, in support of research in the particular focus area of those organisations.

Table 9 Third party funding contributions to the programme

Funder	***Amount***	***Modality***	***Focus***
Dutch Cancer Society	€ 1.1m	Personalised medicine	Oncology
Dutch Arthritis Foundation	€ 1.1m	Personalised medicine	Rheumatology
Netherlands Heart Foundation	€ 2.5m	Large Multicentre Trials ; rediscovery	Heart failure, atrial fibrillation
Canadian Institutes of Health Research	€ 3.5m	Personalised medicine	Rheumatology
Zilveren Kruis Achmea	€ 3m	Personalised medicine	Oncology and rare disease
Total	**€ 11.1m**		

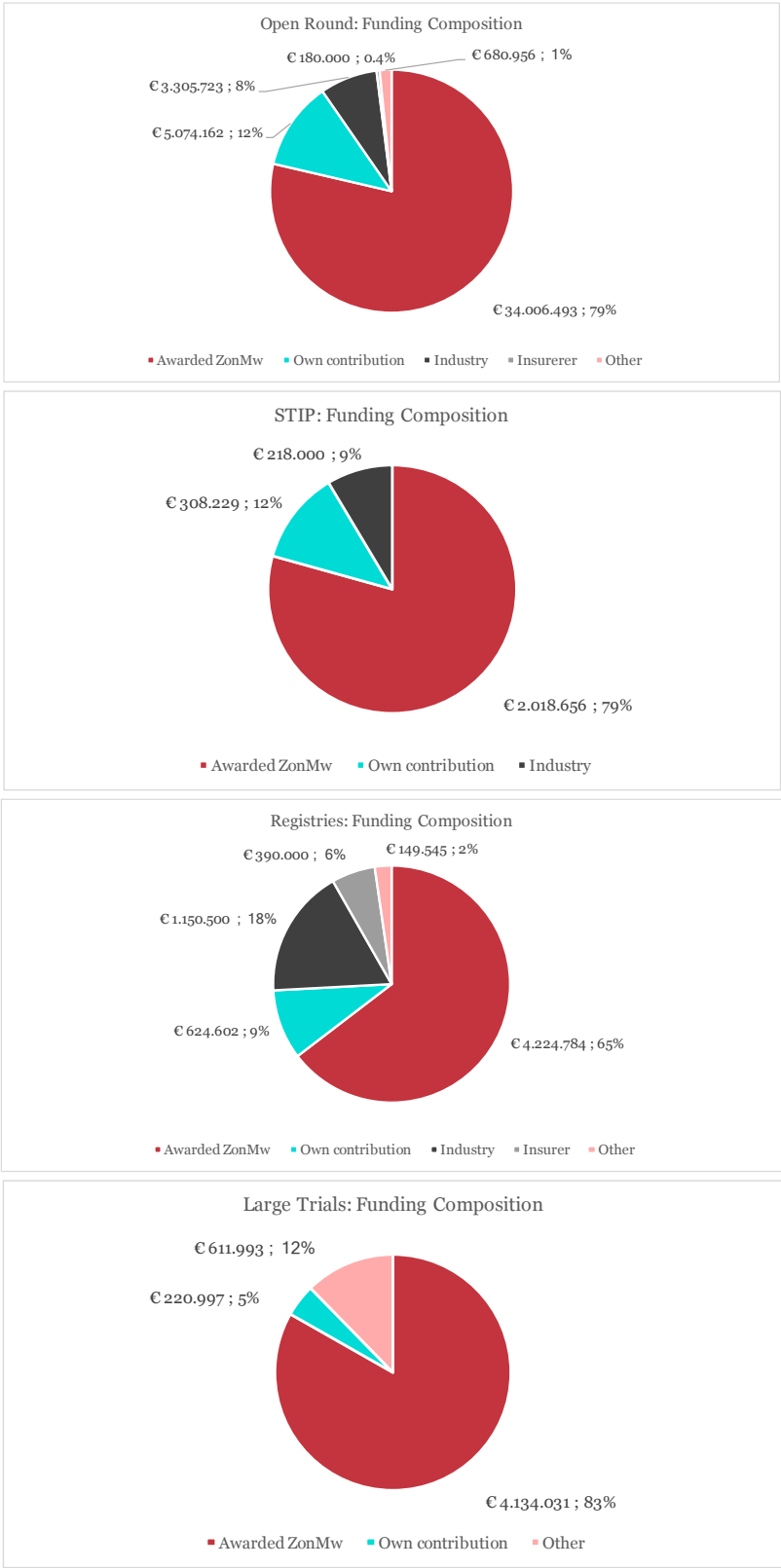
Interviews with the programme office, members of the programme committees and other stakeholders suggest that the current composition of the total funding of projects does not correspond with initial expectations of third party contributions. Whilst among some stakeholders there is a feeling that the pharmaceutical industry should be a greater contributor, others have noted that any such involvement could represent a serious risk of conflict of interest and could jeopardise the independence of the research.

Also the collaboration between the GGG-programme and the insurers has proven difficult. Within the programme there had been initial expectations that insurance companies, either individually or collectively, would contribute co-financing. However, from the perspective of the insurers, at that time

[4] The term 'Room' refers to the GGG-programme house presented in section 2.2.

the contents of the programme appeared to have already been largely decided. This left the feeling that the programme was only seeking financial contributions and did not consider the insurance companies as stakeholders to be meaningfully involved in determining a strategic course. Furthermore, the insurers did not have a mechanism for disbursement of non-competitive funding. Consequently, the financial contributions of insurance companies have been slow to take off. The lack of direct involvement of insurers is also reflected at the level of the GGG-council where they are no longer represented. More recently, however, individual insurance companies have become more engaged, either at the project level or by supporting programme elements. Zilveren Kruis Achmea, for instance, now provides co-funding in the Personalised Medicine modality to support research on oncology and rare diseases. Greater involvement of insurance companies, both as financiers and as advisors (through the GGG council or the programme committees), would be welcomed by several interviewees, who consider them important stakeholders in issues of rational pharmacotherapy. At the same time, a similar risk of conflict of interest could arise as with industry participation. Insurers themselves indeed express some reservations about such involvement, at least in part, because they do not wish to be perceived as influencing the direction of research. To mitigate any such risks, ideally any financial contributions from either insurers or industry should come in the form of programme-level support, such that the funding contributor for a research project has no direct stake in the outcomes of that research.

Figure 3 Funding composition by source



Source: Technopolis 2017, based on ZonMw data

4.2 Project selection

4.2.1 Selection process

The assessment of project ideas and proposals submitted within the GGG-programme is organised according to the 'standard' ZonMw procedure (Appendix I). Interviews with project leaders highlighted that this process was clearly communicated by ZonMw.

Applicants are invited to respond to a call for proposals by submitting an initial project idea. These project ideas are assessed by the programme committee and patient panel on the degree to which they would help achieve better quality and affordable care, on their relevance and specific benefit to clinical practice, and on the extent to which they can be implemented. In addition, it is considered whether and how projects are able to tie in with existing initiatives. Scientific quality is only marginally considered at this stage.

Applicants of project ideas that are considered sufficiently relevant are encouraged to prepare a full proposal. The full proposals are subsequently reviewed by external reviewers, both national and international, by the patient panel and by the National Health Care Institute. Applicants have the opportunity to provide a rebuttal to the review. The reviewer comments and any rebuttals are then discussed in the responsible programme committees. In the final stage of the selection process, the inherent scientific quality of proposals, including study design, is the major deciding factor as relevance is already considered established.

The funding requested for the total of eligible applications has consistently exceeded the budget envelope, such that not all eligible applications can be awarded funding. Therefore, a final prioritisation of projects is made based on an estimation of the potential size and likelihood of impact.

Interviewed project leaders, both for awarded and unsuccessful applications, express mixed experiences with the application, review and selection process. The call texts for proposals are generally considered sufficiently clear. However, some researchers struggle with the emphasis on implementation as for certain types of research it is felt difficult to translate results into concrete contributions to practice. Interviewees who attended any of the information meetings organised by the programme for potential applicants found these helpful.

Although the application procedure is clear, several applicants found it overly complex and lengthy, because of the stepped approach. They indicate that, although the project ideas are considerably shorter than full applications, their preparation still requires substantial time investment as they view these as a condensed write-up of a proposal that conceptually has already been worked out.

The degree of satisfaction with the review and decision process varies. In some cases researchers perceived a high degree of 'randomness' in the judgments of reviewers, sometimes compounded by the fact that the number of reviews was small. However, it is recognised this is common in research funding and that this is potentially unavoidable. For the most part, the reviewer comments and the feedback of the programme committee is considered well founded.

4.2.2 Outcomes of selection

Figure 4 shows the number of standing project proposals after each stage in each of the four modalities. The success rate of new proposals, meaning the applicant had not previously submitted (a version of) that proposal in that modality, is 11% for the Open Round. The number of applicants is much higher compared to the other modalities; however, this is also due to a much higher available budget and a broader scope of the calls (Chapter 3). The modality Large Multicentre Trials shows a similar success ratio, namely 7%. The success ratios for the STIP and Registries modalities are notably higher, each at 26%. Although the success ratio for the programme overall – and for the Open Round in particular – may seem low, it is largely in line with that observed in other ZonMw programmes. (Poortvliet, Gagliardi, Lameris, & van Hoesel, 2017).

Members of programme committee for the Open Round indicated that the main reasons for rejecting (full) proposals were related to concerns about the proposed study design and scientific soundness,

rather than to lack of relevance. This is consistent with the staged process outlined before, whereby the relevance of project ideas is established before a full proposal is prepared. Members of the programme committee in the Registries modality noted that, here, proposals often paid insufficient attention to technical aspects, such as appropriate database design and general knowledge of IT infrastructures (discussed in more detail in section 5.2.2).

The programme allowed unsuccessful applicants to resubmit proposals, in a version adjusted to comments of the reviewers and committee, in a subsequent round. Resubmissions occurred only in the Open Round and Registries modality. In the former, resubmitted proposals had a somewhat higher chance of success than new submissions (17% versus 11%), although the number was too small to judge whether this effect is significant. All four resubmissions in the Registries module were unsuccessful.

Figure 4 Application process

Source: Technopolis 2017, based on ZonMw data. (OR = Open Round, Reg = Registries, LT = Large Multicentre Trials)

As mentioned in the preceding section, in every modality – but in particular in the Open Round– otherwise eligible projects have had to be denied funding because the total funding requested exceeded the available budget. One way to narrow the gap between the budget ceiling and the required funding for eligible projects, would be to restrict the scope of the calls. This would likely result in a smaller number of applications, as there would be fewer researchers working within those specific areas preselected for each call. Potential advantages of this are that, first, it would reduce the review burden on the programme committees and the programme office. Furthermore, researchers considering an application can better assess whether their proposals are likely to be considered for funding and, with a

smaller number of competitors, their chances of success would increase. This, in turn, may further incentivise their investment in development of strong project ideas and proposals. However, several interviewees have indicated that they value the more open approach to programming. Project leaders indicated that many of their research projects might not have been accommodated under a narrower research agenda.

4.3 Portfolio composition

How funding is allocated across types of projects and applicants has a direct impact on the extent to which a research funding programme is able to achieve its stated objectives. The following sections therefore describe funding allocation patterns by thematic priority, type of applicant, and project characteristics (medical specialty addressed and target population). Together, these analyses provide an indication of the programme's ability to serve the needs of the field and address urgent questions around rational pharmacotherapy.

4.3.1 Coverage of GGG thematic priorities

As outlined in section 2.2, the GGG programme has been designed around a set of thematic priorities. To assess how well the programme has been able to address each of the thematic priorities, the allocation of project funding across each of the priorities was reviewed within three of the main funding modalities, namely the Open Round[5], STIP, and Registries modalities. For the Large Multicentre Trials modality, no categorisation by thematic priority was done. The other research modalities (Personalised Medicine, Rediscovery and Topdown) were excluded from the analysis as they had only recently started. Educational activities, which are not funded through project calls, were also excluded.

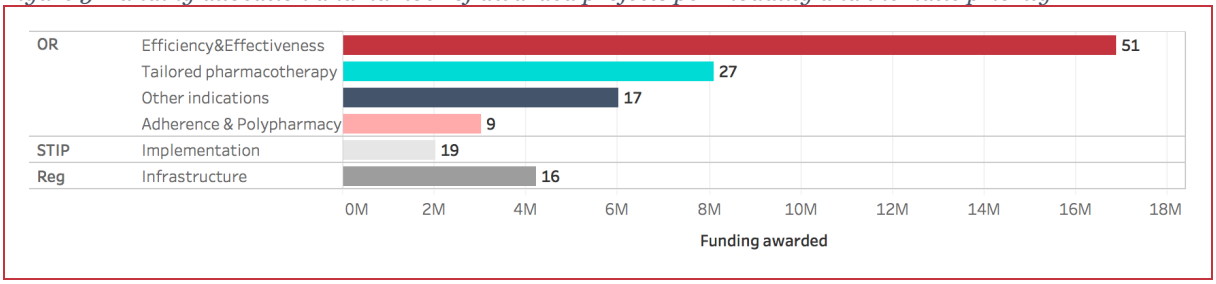
The analysed thematic priorities per modality are thus:

- Open Round
  - Efficiency and effectiveness
  - Tailored pharmacotherapy
  - Other indications, including new formulations and drug rediscovery
  - Adherence and polypharmacy[6]
- STIP
  - Implementation
- Registries
  - Infrastructure

[5] In the process of receiving, correcting and reiterating the data between ZonMw and the evaluation team one update on adjusted funds awarded by ZonMw was not integrated correctly. Therefore, the overall amount of funding in the Opend Round *should* amount to €34.929.281, but in the report on the individual project level amounts to €34.006.493.

[6] The thematic priority 'use & organisation' contains three main subjects, namely therapy adherence, polypharmacy and system organisation. In the categorisation that was done for the purposes of this evaluation, the name 'adherence & polypharmacy' was used instead. A single awarded project had previously been identified as related to system organisation but, simultaneously concerned polypharmacy issues and was reclassified as such. Consequently, whilst throughout this Chapter the thematic priotiry has been named 'adherence & polypharmace', it directly corresponds to the priority 'use & organisation'.

Figure 5 Funding allocation and number of awarded projects per modality and thematic priority[7]



Source: Technopolis 2017, based on ZonMw data

In total, €16.9m of funding has been allocated to projects that address issues concerning the efficiency and effectiveness of pharmacotherapy. In the Open Round 51 projects were awarded in this field. (Figure 5). This is more than twice the amount of funding allocated within the thematic priority 'tailored pharmacotherapy'.

Even more striking is the comparison with thematic areas of 'other indications' and 'adherence & polypharmacy'. Just nine projects were awarded in the latter category, totalling €3.2m. This confirms the perception of several interviewees that the portfolio contains relatively few projects with this focus. Also at the level of the programme office and GGG council the issue is well known and has been previously discussed. A possible explanation offered for this has been that, in comparison to the other thematic areas, the quality of project proposals in this area was often lower. This explanation is at least partially supported by the observation that the success ratio for proposals categorised as 'adherence & polypharmacy' is somewhat lower than that in other areas (data not shown). Also, some interviewees have suggested that, in general, issues in the area of adherence and polypharmacy are relatively complex, and therefore not easily addressed by standard research designs. As this evaluation did not include an assessment of the content or quality of submitted project ideas and proposals, it cannot be established what causes this relative lag. Further examination of this would be needed to remedy this.

The STIP and Registries modality correspond to projects in the thematic priorities 'implementation' and 'infrastructure' respectively. As these modalities have smaller budgets than the Open Round, their lesser representation in the portfolio is unsurprising, and is based on strategic decisions at the programme level rather than an (in)ability to populate the thematic priorities.

4.3.2 Allocation by type of lead organisations and specialisations

The GGG programme is an ambitious programme in the diversity of questions it aims to address. This diversity calls for the involvement of a wide range of actors, across types of organisations and disciplines. Against this background, the funding allocation was assessed against who were the lead applicants and what (medical) specialisation they represented.

It is immediately apparent that most of funding has been awarded to projects with academic institutions (universities and university hospitals) as lead organisation (€36m out of €44m). These projects receive a factor of fifteen more funding and have over tenfold the number of projects awarded, as compared to projects with non-academic hospitals as lead organisation. Together, these organisations are primarily focussed on secondary and tertiary medical care. Organisations that focus mainly on primary care are much less represented in the portfolio. The number of projects awarded, and the amount of funding allocated, is considerably less when the lead organisation was a primary care organisation (€0.8m for 5 projects), whilst only one project was lead by a nursing/home care/rehabilitation facility. This can be partially attributed to the fact that, by nature, these organisations do not normally engage in research. It should be noted, though, that the analysis only considers the lead organisation and these organisations may be involved in projects in another capacity.

[7] For Large Multicentre Trials no thematic priorities were indicated.

In terms of the allocation across medical specialisations, mental health in particular stands out as an area that received aa relatively large amount of funding. This is closely followed by cardiovascular diseases, gastroenterology and primary care. Members of the programme committees, who were invited to comment on the initial findings of the evaluators, indicated that this allocation was largely in line with their expectations. The strong presence of mental health projects was perceived to reflect the fact that mental health is a specialisation where rational pharmacotherapy is a highly relevant topic, due to issues involving the use of drugs with potentially severe adverse effects, polypharmacy and poor adherence. No explicit rationales were given for the relative positions of other areas.

It is worth noting that, even though primary care organisations are not strongly represented as lead organisation, as a medical specialisation, primary care was still found to be an important focus of the programme. However, these projects are mostly led by academic departments for (research in) primary care. The fact that most research in primary care is led by academic institutions need not be surprising, as it is rare for primary care practitioners to be engaging in research themselves. Nonetheless, several interviewees have expressed a desire to see stronger involvement of primary care organisations and other parties that are in direct connection to the field, such as community pharmacists. They express that this is necessary to improve the working across care boundaries and place greater focus on the patient journey. Their involvement is also essential to support implementation of findings into practice. The programme office has indicated that it has attempted to further engage primary care organisations, but that the lack of research infrastructure and capacity here remains an obstacle.

Figure 6 Allocation of funding by type of lead organisation per modality and specialisation

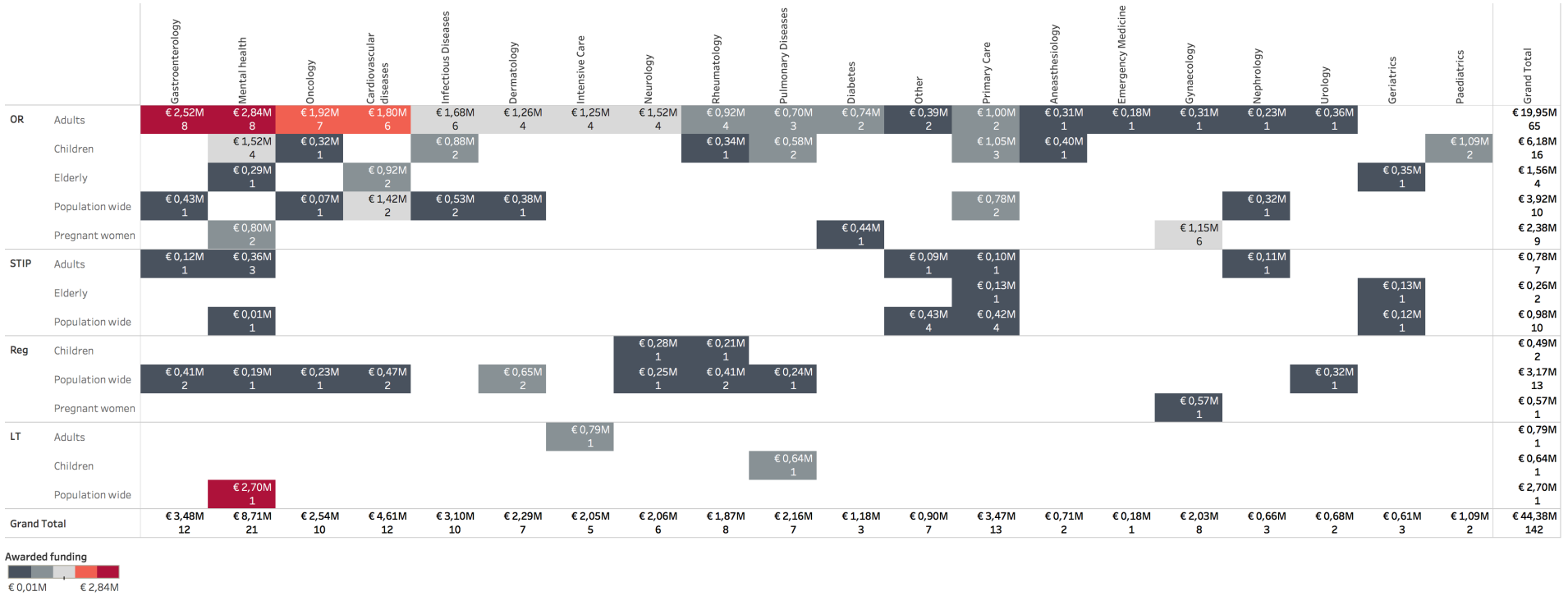
Source: Technopolis 2017, based on ZonMw data

4.3.3 Target groups and specialisations

Another characteristic of the GGG-programme analysed is whether the programme addresses pharmacological issues for a wide range of target groups (Figure 7). Most of the funding awarded in the Open Round went to projects that focused on adults and children. For the STIP modality, projects targeting the entire population and adults received the most funding. In the Registries modality funding is distributed over projects targeting the entire population, children and pregnant women. The three projects in the Large Multicentre Trials modality each have a different target group.

External stakeholders and the programme office expressed concern that research focussing on care for elderly people is insufficiently catered for within the current project portfolio. Interviewees feared that, due to the complexity of elderly care, researchers would be less inclined to submit proposals and that submitted proposals would not meet the criteria. These concerns are, to a degree, supported by our analysis. Across all modalities, only six projects have been awarded that specifically target elderly care. It is possible, though, that in some instances this group was still a target population but that, because of a broader scope of the project, the project was categorised as targeting the entire population or adults. Other interviewees have suggested that the perceived underrepresentation of elderly care might have to do with the overall lagging of polypharmacy as a study field. No issues were raised in any of the interviews about the degree of representation of children and pregnant women as target groups in the project portfolio.

Figure 7 Allocation of funding by target group per modality and specialisation



Source: Technopolis 2017, based on ZonMw data

4.3.4 Unsuccessful applications

To determine whether some of the observations made concerning the composition of the portfolio are a reflection of the overall applications or whether certain project characteristics can be linked to the chance of receiving funding, also the composition of unsuccessful applications was reviewed. Unsuccessful applications are herein defined as all projects that were rejected at any of the stages of the selection process (that is, initial applications, full proposals and eligible proposals that did not receive funding) (Figure 8).

By far, the highest number of unsuccessful applications (643) comes from projects led by academic institutions. This is foremost a reflection of the total number of applications from these institutions, since, at 14%, their average success rate is comparable to that of non-academic hospitals (13%), primary care organisations (15%), and (semi)governmental organisations or regulatory bodies (14%). Mental health organisations had the highest probability of success (23%).

Several external stakeholders, programme committee members and the programme office have voiced concern about the perceived lack of presence of primary care organisations among lead applicants. Questions were therefore raised whether the problem rests in attracting applications from these organisations or whether they tend to be less successful in the selection process. The above analysis suggests that, overall, primary care organisations are not less successful than other organisations. Particularly in the STIP modality, which was created to stimulate implementation, primary care organisations have been relatively successful, with four out of 13 applications awarded (31%). This contradicts the feedback from some STIP committee members who expressed the impression that primary care organisations are often not as well equipped to design and conduct these types of projects. Furthermore, as noted earlier, it is important to bear in mind that even when primary care organisations are not the lead organisation, and thus are not shown in this analysis, they could be involved as project partner.

The uneven distribution across thematic priorities that was observed in the awarded project portfolio is also visible among unsuccessful applications. Of the 757 applications that were assigned to a thematic priority, 42% fell into the category 'effectiveness & efficiency' (versus 37% of awarded projects).[8] Although the relative representation of applications in the area of 'therapy adherence & polypharmacy' is somewhat higher for unsuccessful applications than for awarded projects (15% vs 6%), it remains by far the least populated priority area. This imbalance can therefore not be attributed solely to lower quality of applications (both in terms of scientific quality and of relevance). Rather, despite the fact that many stakeholders observe a knowledge gap in this area, it appears relatively few researchers have translated this perceived need for evidence into research questions.

[8] As discussed, the classification into thematic priorities was done by the programme office for the express purpose of this evaluation. Due to the large volume of applications and limited resource availability, however, not all projects were categorised. It is assumed the uncategorised applications follow a similar pattern to those that were assigned.

Figure 8 Unsuccessful applications: requested funding by type of lead organisation and thematic priority

	OR Efficiency & Effectiveness	OR Tailored pharmacotherapy	OR Adherence & Polypharmacy	OR Other indications	OR Not assigned	STIP Implementation	Reg Infrastructure	GT Not assigned	Grand Total
Academic Institution	€ 102,25M 265	€ 48,13M 128	€ 26,30M 79	€ 16,89M 48	€ 13,19M 46	€ 1,29M 11	€ 4,07M 31	€ 51,76M 35	€ 263,89M 643
Hospital (non-academic)	€ 7,44M 24	€ 5,36M 20	€ 0,40M 2	€ 1,71M 7	€ 2,09M 9	€ 0,18M 2	€ 0,33M 3	€ 1,13M 2	€ 18,65M 69
Research institute	€ 3,49M 9	€ 2,48M 5	€ 6,07M 13	€ 0,15M 1	€ 0,74M 3	€ 0,28M 3	€ 0,54M 4	€ 3,89M 2	€ 17,65M 40
Mental Health Organisation	€ 2,48M 8	€ 0,28M 1	€ 1,56M 7		€ 0,63M 3	€ 0,53M 5			€ 5,47M 24
Primary Care	€ 1,16M 3		€ 0,89M 4	€ 0,54M 1	€ 1,92M 10	€ 0,77M 9	1		€ 5,27M 28
(semi)Government & Regulation	€ 0,98M 2	€ 0,73M 3	€ 0,36M 1		€ 1,62M 5	€ 0,10M 1			€ 3,79M 12
Nursing Home, Home Care or Rehabilitation Facility	€ 0,84M 3	€ 0,45M 2	€ 0,60M 1		€ 0,47M 3	€ 0,77M 8			€ 3,13M 17
Higher Vocational Education	€ 0,74M 1		€ 0,24M 1			€ 0,21M 2			€ 1,19M 4
Patient/consumer organisation	€ 0,45M 1	€ 0,28M 1	€ 0,28M 1		€ 0,24M 2	€ 0,10M 1			€ 1,35M 6
Professional Association	€ 0,42M 1	€ 0,25M 1	€ 0,19M 1		€ 0,60M 3	€ 0,21M 2		€ 0,45M 1	€ 2,12M 9
Centre of Expertise		€ 1,72M 4	€ 1,05M 4	€ 0,46M 1	€ 1,33M 6	€ 0,53M 5	€ 1,42M 6		€ 6,51M 26
Other	€ 0,50M 1	€ 0,40M 1	€ 0,02M 1	€ 0,56M 1	€ 0,57M 2	€ 0,71M 5			€ 2,77M 11
Grand Total	€ 120,73M 318	€ 60,08M 166	€ 37,96M 115	€ 20,30M 59	€ 23,42M 92	€ 5,70M 54	€ 6,36M 45	€ 57,24M 40	€ 331,80M 889

Source: Technopolis 2017, based on ZonMw data. (Some applications were unintentionally not assigned to a thematic priority.)

5 Programme results

This chapter presents the results generated by projects funded under the GGG-programme and its predecessor programmes, as well as their realised and expected impacts.

To better understand what the GGG-programme has yielded so far in terms of research findings and subsequent contributions to practice, a result analysis was done using two main methodologies. First, we analysed responses to a survey developed and administered by the programme office that collected (self-reported) data on outputs, outcomes and impacts of the projects. Second, we reviewed available project documentation (proposals, progress reports and final reports) for a selection of projects. The two methodologies are described in more detail in Appendix F.

Throughout this chapter, the findings from the two methodologies are, where applicable, integrated. Consistent with the logical framework developed for this evaluation, we respectively review the activities (that is, research conducted), the outputs produced, outcomes (research findings) and impacts. Both realised and, where appropriate, anticipated results are discussed.

5.1 Project characteristics

Using both survey data and data from the project documentation, we have analysed various characteristics of the project portfolio, as discussed in the following sections.

5.1.1 Research design

To better understand the *type* of research conducted under the programme and the strength of the evidence generated as a result, we reviewed the study design and methodologies proposed in the selected 26 projects. We distinguished between three main typologies: experimental studies, observational studies, and all other study designs.

In experimental studies one or more factors are subject to intervention by the researchers. An intervention could, for instance, be the delivery of a new drug or a change in treatment. Experimental studies can be either controlled or non-controlled (as is typically the case in pilot studies) and allocation to intervention or control arms can be done with or without randomisation. Observational studies, by contrast, do not involve the introduction of a new intervention but – as the name suggests – observe the effects and impacts of *existing* clinical practice. Observational studies are mainly used when it is not possible to conduct experimental studies because of, for instance, practical or ethical reasons. Whilst the evidence generated by controlled experimental studies is considered stronger, because bias and confounding are limited, observational studies have the advantage that they more closely reflect daily practice. Within this programme both types were found. Additionally, the selection includes projects that could not be neatly classified into these two categories. Those are primarily projects where the aim was to develop new models or indicator sets, or to set up patient registries.

It is noteworthy that of the 26 projects analysed here, the majority (15 out of 26) included an experimental study design (Table 10). Moreover, of the projects awarded in the Open Round half (9 out of 18) were based on, or at least included[9], a randomised controlled trial (RCT) in the initial project design.[10] In medical research, the RCT design is widely considered the 'gold standard of evidence'. Whilst the choice for a particular study design will be guided by the nature of the research question, the presence of a significant number of RCTs in the portfolio may also correlate with the importance attributed by the programme committees to scientific rigour. Because it is considered more robust, evidence generated through RCTs is more likely to be taken up in clinical guidelines and practice. From

[9] Many projects involve multiple phases, each of which follows a different study design. A study was counted as 'experimental' if it included at least one component that used an experimental study design.

[10] In at least one of the analysed projects, the initial RCT design was subsequently abandoned due to problems with inclusion of patients into the study. The study was continued as a cohort study.

that perspective, the focus on RCTs is consistent with the aim of the programme to contribute to uptake of evidence in clinical practice. However, despite their great value, RCTs and other experimental designs present several challenges.

First, to reach statistical significance, experimental studies that involve allocation of patients over multiple study arms require a sufficiently large number of patients. Particularly for studies in rare diseases, with small numbers of patients, it is often difficult to identify enough eligible patients who are willing to participate. Indeed, inclusion problems were frequently mentioned in interviews with the programme office, members of the programme committees, and project leaders. We are aware of four projects that were terminated prematurely due to insufficient patient enrolment and several more where similar problems resulted in severe delays or necessitated modifications to the study design.

Second, within the Dutch health research funding landscape the GGG programme is rare in its focus on rational use of medication *in practice*. One could thus argue that the programme should also provide sufficient space for research conducted under pragmatic trial conditions. By this we mean that experimental trials often, and necessarily, have stringent inclusion and exclusion criteria to select trial participants to reduce and control for confounding. As a result, trial participants may not be representative for the entire patient population. Observational study designs may be better equipped than experimental studies to produce results that have greater generalisability. However, interviews with project leaders suggest that applicants sometimes feel pressured into framing their research questions around an experimental design, to increase their chances of being funded, even when they anticipate difficulties with this set-up.

Last, the apparent emphasis on experimental studies may mean that some questions that are less suited to experimental designs remain unaddressed. For instance, research questions in the space of personalised medicine by nature do not lend themselves well to standard clinical trial designs. It has been suggested that the lack of projects with a focus on polypharmacy can be, partially, explained by the fact that –because of the heterogeneity of the patient population – this research does not lend itself well to study designs that attempt to exclude all possible confounding rather than correct for it. However, the extent to which design considerations have influenced the composition of the current project portfolio is unknown.

Table 10 Study design of selected projects, per modality

Programme	Experimental		Observational	Other
	RCT	Non-RCT		
Open Rounds	9	2	6	1 (Modelling)
STIP	-	2*	1	
Patient registries	-	-	-	2
Large Multicentre Trials	-	-		
DO Pharmaco / DO PMK	2	-	1	
Total	**11**	**4**	**8**	**3**

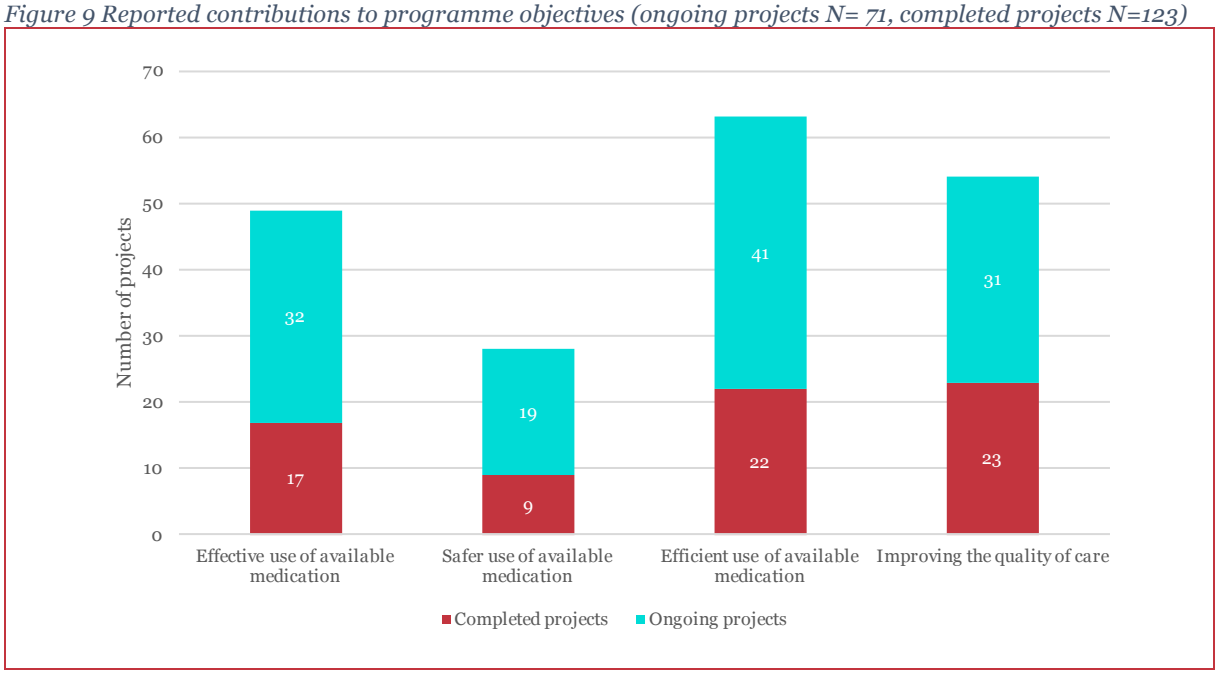
Technopolis Group 2017, based on documents provided by ZonMw. *1 non-randomised, 1 non-controlled

5.1.2 Contribution to programme objectives

Survey participants were asked which of the programme objectives their projects had contributed to, or were expected to contribute to, most. We note that these are the goals of the GGG-programme, and therefore are less applicable to the predecessor programmes. Contributions to more efficient use of available medication was most often mentioned as the primary project objective (Figure 9). As only one answer was allowed, there may be underreporting on more “downstream” goals. Indeed, several

respondents indicated as such. Response categories did not include 'no contribution', but five participants commented that their project did not contribute to any of the goals.

Figure 9 Reported contributions to programme objectives (ongoing projects N= 71, completed projects N=123)



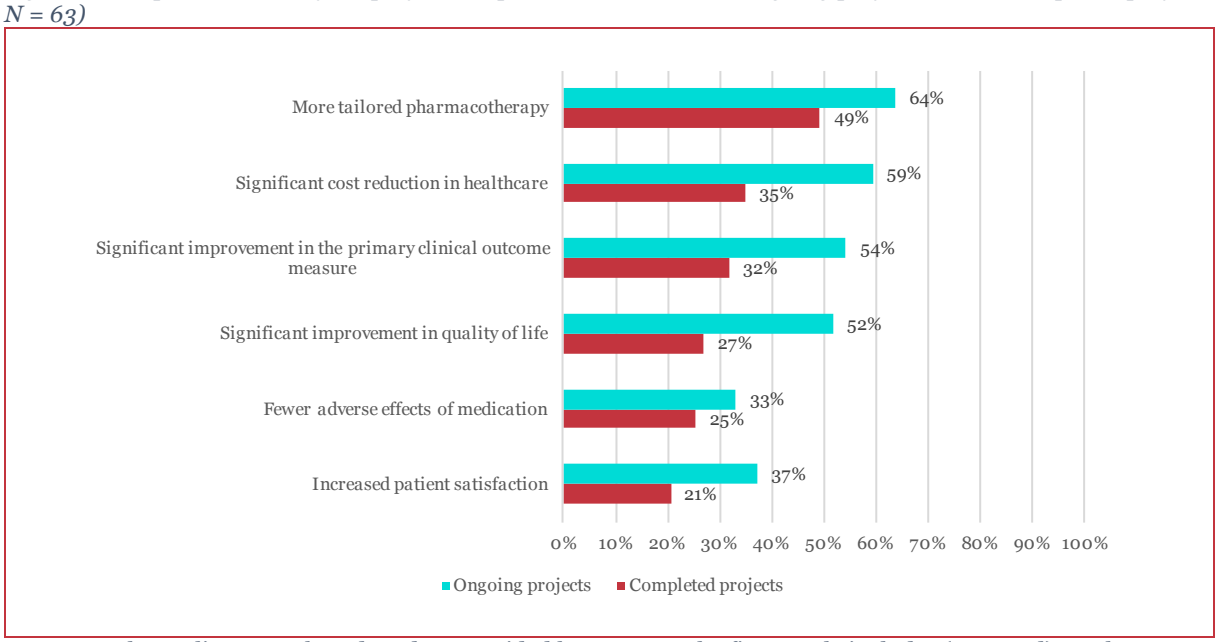
Source: Technopolis Group, based on data provided by ZonMw

5.1.3 Impact pathways

Survey participants were asked in what areas they expect their projects to impact health care. The majority expect to contribute to better tailored pharmacotherapy (Figure 10).[11] Furthermore, they frequently expect their projects to result in cost reductions, improvements in primary clinical outcome measures and improved quality of life. Responses not shown were: fewer adverse drug effects (11% for completed projects and 14% for ongoing projects), fewer prescription errors (10%), fewer errors in drug administration (5% and 8%), fewer contra-indications (6%), fewer errors in transfer of medication data (3%) and fewer errors in preparing medication for administration (3%).

[11] For simplicity, only the most frequently occurring response categories are shown in the figure.

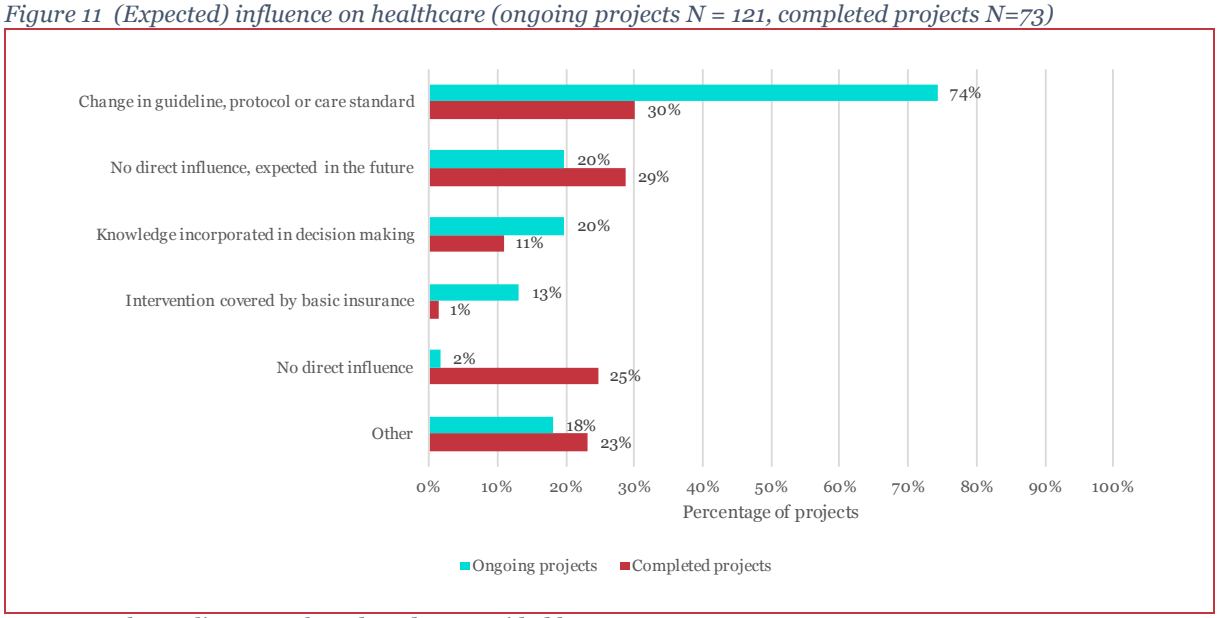
Figure 10 (Expected) result of the project compared to current care (ongoing projects N=118, completed projects N = 63)



Source: Technopolis Group, based on data provided by ZonMw. The figure only includes (expected) results >20%.

Survey participants were also asked *how* they anticipate their projects have influenced, or will influence, healthcare. Of the 194 respondents, the majority anticipate their projects will result in a change to guidelines, protocols or care standards (Figure 11). There is a clear difference in expectations between project leaders of completed and still ongoing projects on the uptake of the results of the study in guidelines, protocols or care standards (30% versus 74%). This is supported by the finding that, 25% of project leaders of completed projects indicated their projects have had no direct influence on healthcare. This is, in part, a natural outcome of the fact that project leaders for completed projects already are able to assess whether their findings have had, or are likely to have, an impact. For unsuccessful projects, or projects were research findings did not warrant any change to existing practice, the likelihood for impact strongly decreases or even falls away.

Figure 11 (Expected) influence on healthcare (ongoing projects N = 121, completed projects N=73)



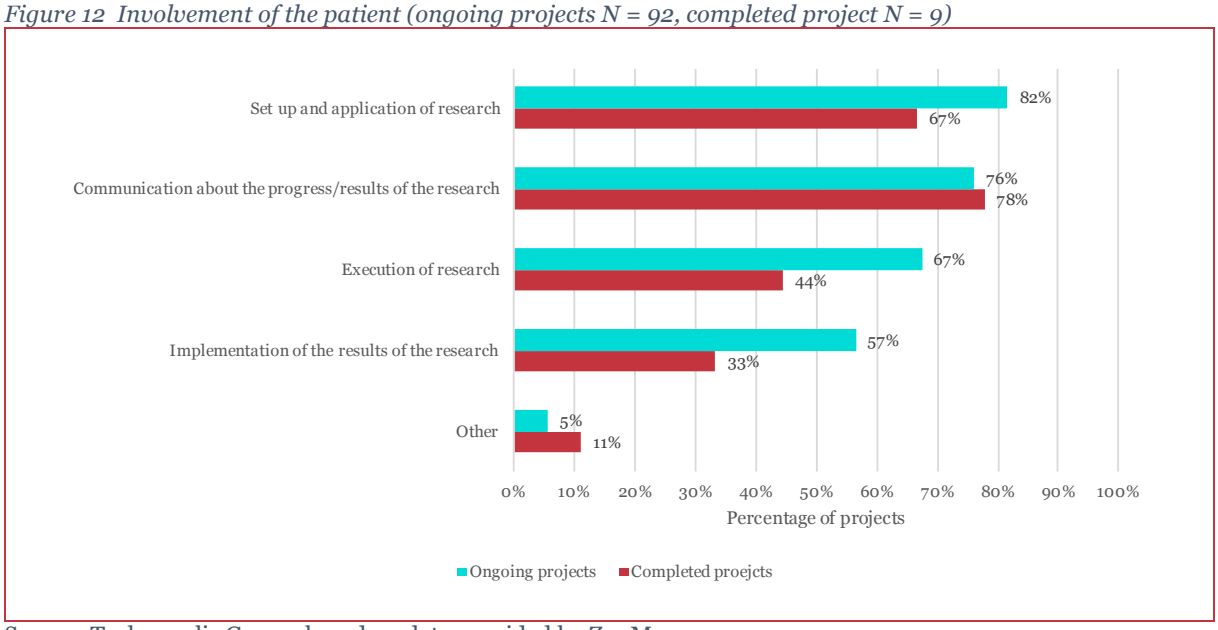
Source: Technopolis Group, based on data provided by ZonMw

5.1.4 *Patient involvement*

Project leaders were asked at what stages of their projects patients had been, or would be, involved. Within the GGG programme patient involvement has been an explicit requirement. Predecessor programmes did not have this requirement and data from these projects were thus excluded from the analysis.

Patients were involved in GGG-projects in multiple ways: as recipients of communication outputs, as advisors in the set up and implementation of projects, during the execution of the research (as 'test' subject) or as (potential) users of the research results (Figure 12). Some respondents commented that patient involvement in their project was not considered appropriate, for example when the study concerned patients with severe dementia.

Figure 12 Involvement of the patient (ongoing projects N = 92, completed project N = 9)



Source: Technopolis Group, based on data provided by ZonMw

5.2 Outputs

5.2.1 *Publications and presentations*

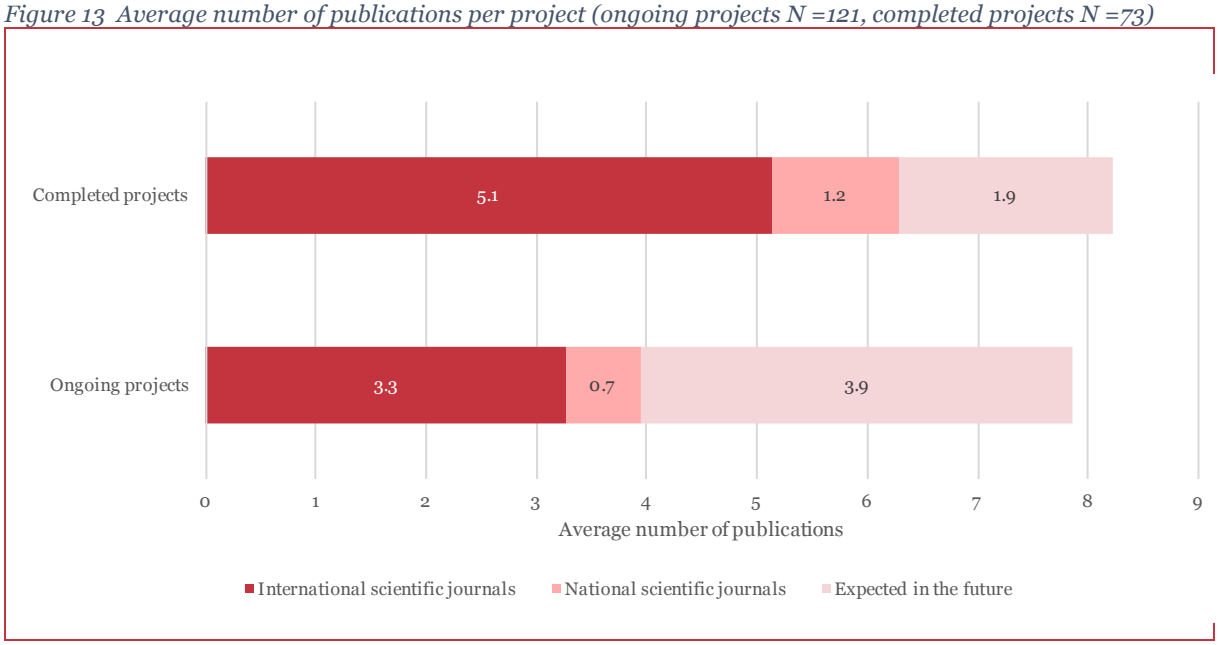
As a research funding programme, the primary outputs of the programme include scientific publications, theses and publications on conferences. Survey data show that, on average, projects resulted in 5.1 publications in international scientific journals for completed projects, and 3.3 for ongoing projects (Figure 13). A further 1.9 and 3.9 publications respectively are still expected, totalling an average of seven publications per project. These numbers are somewhat skewed by a small number of projects with a very high number of publications. To date, respondents listed a total of 768 publications in international scientific journals, 165 publications in national scientific journals and 615 further expected publications.

About one-third of projects (23% completed projects, 36% of ongoing projects) resulted in an article in a newspaper or non-scientific magazine or in the newsletter of a patient association (both around 30%) (not shown). Relatively few projects resulted in publication of book chapters or publicly available reports (both about 12%).

Both completed and ongoing projects are expected to result in an average of one dissertation per project (not shown). Furthermore, 29% of project leaders from completed projects and 67% of project leaders from ongoing projects anticipate that their project will result in additional dissertations. Around 16% of

the projects did not result in dissertations. The total number of published dissertations thus far is reported as 176.

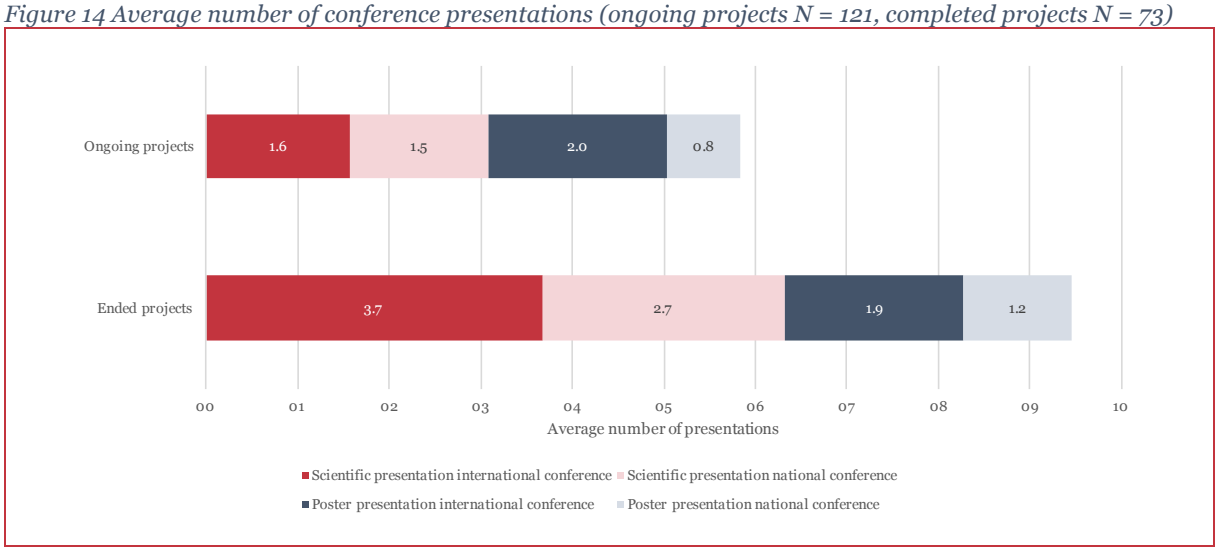
Figure 13 Average number of publications per project (ongoing projects N =121, completed projects N =73)



Source: Technopolis Group, based on data provided by ZonMw

Most presentations given on completed projects were at international conferences (Figure 14). Some projects represented outliers with 15 to 40 presentations. Many projects (52% of completed projects, 72% of ongoing projects) also were presented to carers, patients or research groups. 13% of completed projects and 10% of ongoing projects resulted in presentations for radio and television.

Figure 14 Average number of conference presentations (ongoing projects N = 121, completed projects N = 73)



Source: Technopolis Group, based on data provided by ZonMw

More such scientific outputs will continue to be generated within both already completed and still ongoing projects, as there is often a time lag of many months or even years before study results are published.

5.2.2 *Patient registries*

The Registry modality specifically supported the development, implementation and, ultimately, scale-up of patient registries. Appendix H presents an overview of awarded patient registry projects, their lead organisations and project status.

In principle, each of these projects should contribute to the creation and further development of a patient registry. The majority, however, is still ongoing. In the three projects thus far completed, the developed registries are in different stages of implementation. The Pregnancy Drug Register developed by Lareb is operational, and efforts are ongoing to scale-up use of the registry nationally (Figure 15). A registry for chronic hepatitis B and C patients has similarly been validated. Discussions with stakeholders on further implementation are ongoing. Last, the DAiRE registry for patients with SLE has been operational since 2015 but, due to software problems, has had to be ported to a new system.[12] It is anticipated that the register will continue operations after this migration has been completed.

Figure 15 The Pregnancy Drug Register

Pregnancy Drug Register

The GGG-module Registries provided a good opportunity for the Netherlands Pharmacovigilance Centre Lareb to carry out a study on the safety of medical drug use during pregnancy. The many questions the centre received on this topic showed that there was a clear need to better understand the safety and risks involved when using medical drugs during pregnancy.

To address these questions, Lareb developed and implemented a national register for prescription and over-the-counter medical drug use during pregnancy and for pregnancy outcomes such as miscarriage, stillbirth, birth defect, low birth weight and preterm delivery.

The project resulted in the set-up of an IT infrastructure that monitors the use of medical drugs in pregnancy and during breastfeeding. The register is developed in such a way that in the future it can also be used to conduct analyses in sub-groups, such as women with certain conditions. Moreover, the register provides data for further research.

Ultimately, the project aims to have a national coverage and a wider inclusion of pregnant women. This will also automatically enlarge the scope of research possibilities.

Source: Technopolis 2017, ZonMw data, interviews.

Because most registry projects are still ongoing, and those registries that have been completed are still in early phases of implementation, it is not yet possible to determine their contribution to rational pharmacotherapy in practice. Members of the programme committee Patient Registries have indicated that, currently, among stakeholders like the National Health Care Institute the use of the data from the registry projects is limited. This may also be because the registries are not always accessible to external parties. However, the primary contributors to the registries will be health professionals and, in some cases, patients. Their willingness to contribute is dependent on many factors and needs to be assessed on a case by case basis once registries are fully operational.

A concern expressed by some interviewees is that the registries currently being developed insufficiently track the full patient journey. This transmural approach requires participation of health professionals at all applicable levels of care. The programme has tried to emphasise primary care more, and in the fourth round two transmural registry projects were financed. However, in general, project proposals from this field were said to have been of lesser quality.

The utility and sustainability of the registers will depend on continued financial and technical support. Particularly technical support may prove pivotal. Members of the programme committee observed that, especially in earlier calls, many applicants had limited understanding of technical challenges, such as data management and protection of patient privacy. Although it is felt to be improving, the worry is that lack of technical know-how results in too many ad hoc solutions that are not sustainable in the longer-term. One interviewee suggested that ZonMw could play a greater role in standardisation of registries

[12] http://www.dairegistry.nl/

and in coordinating their national implementation. Furthermore, many project proposals were said to be driven by existing clinical questions, and were not designed as broad-based infrastructures that could be used to address new questions as they emerge. This question-driven approach, as opposed to an infrastructure-driven approach, could limit the utility of the registries and thereby negatively impact their sustainability.

Although the above listed projects specifically focused on development of infrastructures for data collection and analysis, projects funded in other modalities also can include the creation of technical infrastructures, such as a database containing genotypic and phenotypic data for patients with Fabry disease (Figure 19).

Figure 16 Optimising therapy for patients with Fabry disease

Individualised treatment guidelines for patients with Fabry disease

In the first Open Round call, the Amsterdam Medical Centre (AMC) proposed a study to optimise the treatment of patients with Fabry disease, a rare genetic disorder.

There was an acute reason for this study as there was a serious lack of high quality, long-term data on the duration of the expensive treatment of Fabry disease (Enzyme Replacement Therapy - ERT). The lack of knowledge on when to stop medication for certain groups of patients has led to an extremely unfavourable cost-effectiveness profile which raised questions on the reimbursement of the treatment.

The study, in collaboration with two leading Fabry treatment centres in London and Wurzburg, retrospectively analysed the data of 600 patients.

Different patient characteristics were identified that have an effect on the treatment of the Fabry disease with ERT. Currently, refinement of specific treatment criteria for different types of Fabry patients is ongoing.

The relevance of the GGG-programme was underscored by the project leader, who stated that pharmaceutical companies dominate the research on Fabry treatments and that independent research is much needed. The project further created a strong European network around Fabry disease and provided multiple additional insights in addition to the main research questions.

Source: Technopolis 2017, ZonMw data, interviews.

5.2.3 GGG conference

To date, the programme office has organised between two to seven meetings with stakeholders every year. Additionally, programme staff has presented the programme or results at one to seven meetings annually (Appendix K). These meetings include information sessions with potential applicants, workshops with GGG-project leaders and expert meetings.

The programme office also organises an annual GGG conference, open to everyone interested. It provides an opportunity for stakeholders to learn about the results of GGG-projects (and other innovative projects) and to discuss relevant rational pharmacotherapy topics. The conference also provides an opportunity to meet other stakeholders and to exchange knowledge. So far, five conferences have been organised (2013 – 2017). Since 2015, these conferences each have had a theme ('Custom Therapy' (2015), 'No more and no less' (2016) and 'Today's knowledge = inspiration for tomorrow' (2017)). The conferences include speeches by high-level people (such as the minister of VWS, the chairman of ZonMw, the director of the Dutch Cancer Society, and renowned academics), parallel sessions, poster presentations, and a networking session.

Attendees to the GGG-conference come from many different organisations. They include researchers, (hospital) pharmacists, health care practitioners (medical specialists, general practitioners and nurses), policy makers, health insurers, people from umbrella associations and patient organisations, people working for pharmaceutical companies, and other organisations.

Many interviewees have indicated they had attended at least one GGG conference, either as a visitor or as a speaker. They view the conference as a major strength of the GGG-programme that contributes to the formation of networks and ideas and enables people to have a better overview of the programme as a whole.

5.2.4 Research collaborations and networks

Research infrastructures include not only physical or technical (IT) structures, but also networks and collaborations of various stakeholders and organisations. Multiple project leaders who were interviewed in this evaluation, for instance, pointed towards formation of new collaborations, including with non-traditional parties.

> *For this study we brought together practically the entire country, that is fairly unique! We don't often do that for these kinds of studies. Most of the time studies are divided of clusters of centres. (Project leader of awarded project)*

When looking at the collaborations that occurred within the GGG-programme, there are a few observations. Due to the large volume of projects and consequent involved parties we have chosen to focus on analysing collaborations between types of organisations, rather than individual actors themselves. To do so, we have defined thirteen different types of organisations, namely:

Table 11 Overview of types of organisations

Organisations
Centre of Expertise
(semi) Government & Regulation
Hospital (non-academic)
Insurer
Mental Health Organisation
Nursing Home, Home Care or Rehabilitation Facility
Patient/consumer organisation
Primary Care organisation
Professional Association
Research Institute
University
University Medical Centre
Other

Considering the high number of project proposals, it is unsurprising that the University Medical Centres (UMCs) collaborate also a lot amongst themselves. Additionally, the research institutes also often collaborate with UMCs, and to some extent with professional organisations such as those of general practitioners or pharmacists. There is a high degree of collaboration between patient consumer organisations and non-academic hospitals and mental health organisations, in addition to the UMCs. Primary care organisations collaborate mostly with universities and with UMCs.

As already noted several times, some parties have expressed concern about the degree to which primary care organisations are (not) involved in the projects. Previous analyses only focused on which institutions were the project leader, potentially obscuring the role of primary care organisations. We observe that in 14% of projects primary care organisations participate in at least some capacity (project leader, project support, expert, etc.). This ranks them behind UMCs, non-academic hospitals, universities and research institutes, all of whom are better equipped and more explicitly tasked with research. Moreover, not all projects are of direct relevance to primary care organisations.

It remains somewhat unclear to what extent the programme is aligned with other initiatives involving rational pharmacotherapy. The programme office indicates that it has looked at relevant developments

in countries such as Belgium, the UK and the USA, but for the moment that has not resulted in any changes to the design or objectives of the programme, nor have there been any structural international collaborations. The ongoing collaboration with the Canadian Institutes of Health Research is tied to a single call. Although initiatives abroad are certainly worth monitoring, many of the problems around rational pharmacotherapy are greatly influenced by the context of national health care systems. As such, there currently does not appear to be an urgent need for greater international collaboration or alignment at the programme level.

5.3 Outcomes

Outcomes for the selected projects for in-depth review are summarised below and structured according to 'thematic priority'.

5.3.1 Efficiency and effectiveness

Among selected projects focused on improving efficiency and effectiveness, four projects are still ongoing[13] and no results are available yet. Six projects have been completed, of which three were granted under the Open Round and the other three originated in the predecessor programmes. For the ongoing projects, their objectives, study approach and – where available – preliminary results are summarised in Appendix G. The main results of completed studies and, where known, the way in which these have since been taken forward, are summarised below.

- One project (Project 836011007) looked at the long-term effectiveness of treatment with TNF inhibitors in patients with rheumatoid arthritis in daily clinical practice. Based on comparison of different medications, **improved recommendations on preferred treatment** could be formulated in the form of decision trees.
- The PanAm study (project 836011015) looked at the effectiveness and safety of treatment of pain in patients with traumatic musculoskeletal injuries with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs). It found no significant differences in decrease of pain scores or side-effects in any of the three studied intervention groups, suggesting **no benefit of treatment with NSAIDs or a combination of both drugs over treatment with paracetamol alone**.
- The aim of project 836021007 was to develop a **list of indicators for diabetes care** to better measure quality of treatment (Figure 20).
- Babies who experience an oxygen deficit at delivery are commonly treated with controlled hypothermia to reduce the risk of brain damage. However, this in turn can reduce the effectiveness of other medications. The PharmaCool study (project 113201001) studied the pharmacokinetic and –dynamic (PK/PD) properties of different groups of drugs in new-borns undergoing therapeutic hypothermia. Based on its findings, **new dosing regimens have been suggested**.
- Treatment with Tumour Necrosis Factor inhibitors (TNFi) in patients with rheumatoid arthritis (RA) is extremely costly and long-term treatment may have negative impacts on a patient's overall health. Therefore, a study (project 152041001) was set up to assess the possibility of reducing or even stopping TNF inhibitor treatment in patients who have been in remission for a certain time. It was found that, in a significant number of patients, treatment with TNFis could be stopped for prolonged periods of time.
- The DECS study (project 170885602) was designed to study the cost-effectiveness of dexamethasone in patients undergoing cardiac surgery. Purpose of this treatment is to reduce the risk of post-operative complications due to an inflammatory response. Whilst the slight positive effect of dexamethosone was found not significant across the study population as a whole, a clear negative effect was observed in patients older than 75. This finding suggests that the **benefits of**

[13] The status of a project as 'ongoing' or 'completed' is based on the information available in the latest available reporting, as provided to the evaluation team. It is, however, possible that projects have already progressed or even been completed since last reporting.

administration of dexamethasone may be age-related. Further study into this question is required.

In addition to the above discussed outcomes, data provided by the programme office show several more examples of (potential) contributions to more efficient and effective use of pharmacotherapy. Outcomes achieved range from better prescription of psychotropic drugs to patients with dementia to findings that, if confirmed, will contribute to safer chemotherapy in children with osteosarcoma.

Figure 17 Increase quality of prescriptions for diabetes patients

Improving chronic medication treatment in diabetes patients

In the Open Round modality, the University Medical Centre Groningen (UMCG) developed a set of indicators to better prescribe medication to patients with type II diabetes.

A number of stakeholders affiliated with diabetes (research) concluded that existing evidence and research surrounding medication prescription to diabetes II patients was outdated. There was a need for a reassessment of the existing list of indicators that assessed the quality of the medication treatment.

The National Association of General Practitioners has been involved from the beginning of the research to ensure new guidelines would be implemented after conclusion of the research.

Source: Technopolis 2017, ZonMw data, interviews.

5.3.2 Adherence and polypharmacy

Of the five selected projects aimed at fostering better therapy adherence or studying issues concerning polypharmacy, to date only two have been fully completed:

- Primary aim of the completed study (project 836011019) was to estimate the cost-effectiveness of multidisciplinary medication reviews to reduce inappropriate polypharmacy in nursing home residents. It found that **a higher percentage of patients receiving the intervention could be taken off at least one drug** as compared to patients receiving usual care (39% versus 30%), with no impact on quality of life.
- Non-adherence to treatment is a significant problem in patients with psychotic disorders. To improve adherence, a Personal Anti-psychotic Choice index (PAKwijzer) was developed, providing selection criteria for antipsychotic drugs based on effectiveness and side-effect profiles (836011004). **The index was found to be user-friendly and effective**, with high patient satisfaction.

For two projects data collection is still ongoing, although some intermediate results have already been reported (Appendix G). One project, that aimed to study polypharmacy in patients with schizophrenia, had to be prematurely terminated due to problems with inclusion of participants for various reasons.

5.3.3 Tailored pharmacotherapy

Two out of six selected projects are currently listed as still ongoing, and for these no outcome results are available yet. Four projects have been completed:

- Patients with Fabry disease, a rare storage disorder, are often treated with enzyme replacement therapy (ERT). ERT treatment is expensive and not effective in all patients, resulting in an unfavourable cost-effectiveness profile. Aim of this project (836011009) was therefore to individualise ERT treatment by identifying factors that affect the response to treatment. Various factors were identified. These findings can be used to **inform treatment protocols**.
- Drug concentrations and effects may be different in obese patients. In this study (project 836011008), the clearance of midazolam, a drug used in treatment of sleeping disorders and in anaesthesia, in morbidly obese patients was studied. Purpose was the **development and implementation of dosing guidelines for midazolam**, and similar compounds, in obese and morbidly obese patients. It was found that, in morbidly obese patients, an oral midazolam dose does not need to be adjusted, while a midazolam intravenous dose should be increased.

- A new model has been developed (project 836011027) to predict absolute treatment effect for patients with medium/high risk on vascular diseases based on simple patient characteristics. This model will help in **identifying patients that benefit the most from treatment**.
- Serious infections with highly resistant bacteria can be treated with intravenous colistin, but evidence based guidelines to ensure effective and safe therapy are lacking. The COLIGO study (836021008) aimed at **evaluating tailored dosing as a way to optimise efficacy and prevent side effects**. It found that in patients with cystic fibrosis controlled dosing led to a high level of effectiveness, while adverse effects were mild.

5.3.4 Infrastructure

The thematic priority 'infrastructure' is made up by projects that were granted in the modality patient registries. An overview of all registry projects and there current status was already discussed in section 3.4.1. Two registry projects were selected for the project analysis. For the DEPAR-R registry for patients with psoriatic arthritis, a central database has already been created and inclusion of patients is ongoing. As discussed previously, the Pregnancy Drug Register (project 836012001) has been completed and is operational. Efforts to scale-up use of the registry are ongoing.

5.3.1 Implementation

Projects in the thematic priority 'implementation' were awarded in the STIP modality that was introduced in 2014. It is therefore not surprising that the three selected projects in this space are all still ongoing. Whilst various activities across the three projects are under way, real contributions to changes in clinical practice are yet to materialise.

For a project aimed at optimising adherence to guidelines for diagnosis, pharmacotherapeutic and psychological treatment for patients in long-term mental health care (project 848022006), at the request of the programme committee, the project period has been extended to cover a longer period to address concerns about feasibility of implementation and continuity. The project has experienced some delays, but has started providing the intervention to enrolled patients with positive results.

5.4 Impacts

5.4.1 Translation into practice

Within the selected projects, 13 projects have been fully completed and sufficient time has passed that impacts may be observable. For such impacts to materialise, it is necessary that research findings have been translated into changes into clinical practice, if the findings indicate such a change is appropriate.

Among these completed projects, several have warranted new, or adjustments of existing guidelines. Specifically, these are:

- The Dutch Institute for Rational Use of Medicine is developing a new **modality for the Pharmacotherapeutic Consultation (FTO)** on pain relief in acute trauma between physicians and pharmacists, based on the findings of the PanAM study (836011015). Within the institution where the study was conducted the recommendations have been implemented.
- Although at the time of last reporting, the results of the POEET study had not been formally translated into clinical guidelines, nearly all rheumatologic centres in the Netherlands had participated in the study (152014001). The finding that, for certain groups of patients with Rheumatoid Arthritis treatment with TNFis, can be reduced is thus widely known within the network and has been **adopted into practice**, although in a somewhat adjusted form (reduction of medication rather than complete cessation). The extent to which the study has resulted in a reduction of TNFi use is unknown to the evaluators.
- The outcomes from a more recent study on treatment of RA patients with TNFi, identifying preferred treatments, are expected to result in an **update of the guidelines of the Dutch Association for Rheumatology**, once results have been published (836011007).

- In the final report of the PharmaCool study, in which new drug dosing regimens were developed for newborns treated with therapeutic hypothermia, it is indicated that for each drug studied the results will be **incorporated in national drug-dosing guidelines (www.kinderformularium.nl)**. This is the main source of information for health professionals on paediatric drug prescription in the Netherlands and is operated by the Netherlands Centre of Expertise for Pharmacotherapy in Children.
- In collaboration with the KNMP new dosing recommendations are being developed for use of midazolam in obese patients and patients who have undergone gastric bypass surgery. These **recommendations, in the form of monographs**, will be published with the KNMP knowledge bank and in the G-standard, accessible to all physicians and pharmacists in the country (836011008).
- Results of the study on identification of patient characteristics that can affect success of enzyme replacement therapy are intended to be incorporated into **revised European treatment criteria** (836011009). This process, which involves deliberations with the European Fabry Working Group and a consensus procedure with international experts and patients, is ongoing.
- Based on the outcomes of the COLIGO study, a **national guideline** for treatment of bacterial infections with intravenous colistin in patients with cystic fibrosis is being developed for the Dutch Working Party on Antibiotic Policy (SWAB) (836021008). Additionally, at the request of the Dutch Association of Hospital Pharmacists (NVZA), a **national guidance document** for Therapeutic Drug Monitoring for intravenous colistin will be prepared.

Last, the overall outcomes of the DECS trial validated current practice in the Netherlands and, as such, do not give rise to a change in guidelines. However, the secondary outcomes that suggest an age-related effect may merit revision to standard care in certain age groups, if validated in further study (170885602).

In addition to informing treatment guidelines and clinical practice, as in the above examples, selected projects have also contributed to the development of clinical decision-making aids and tools for monitoring the effectiveness of treatment. These are:

- The DIM-NHR study, in which multidisciplinary medication reviews for nursing home residents were evaluated, has resulted in the developed of a '**toolbox**' that summarises factors that can facilitate or inhibit 'deprescription' of medication (836011019). This toolbox has been made available for download through ZonMw and will be offered to Verenso – the association for specialists in geriatric medicine – and to the KNMP once the main publication has been accepted. Integration into hospital (pharmacy) software was also recommended but no concrete actions to achieve this are mentioned.
- Although the **Personal Antipsychotic Choice Index** has been validated and was found user-friendly in a study setting, no information is available on its uptake into current clinical practice on a wider scale (836011004).
- A **decision tree,** developed to aid selection of the best TNFi therapy for RA patients, was a secondary study outcome (836011007). There are no indications in the final project report of whether this tool will be shared as a separate output or whether it will be integrated into the recommendations for the new treatment guidelines.

5.4.2 Impact on rational pharmacotherapy and health outcomes

In all of the previously described impacts on translation into practice, we have relied on data from project documentation provided by the office. Throughout the project design and implementation, researchers are required to make explicit in their reporting how they intend to implement the results of their projects. Usually, though, the actions needed to result in uptake of findings are not part of the project. Indeed, whilst the programme encourages researchers to closely involve institutions that develop recommendations and clinical guidelines, such as the medical professional associations, the adoption into practice is a complicated process involving a range of stakeholders other than the researchers. This process therefore only takes place *after* the final reports have been prepared. Whilst

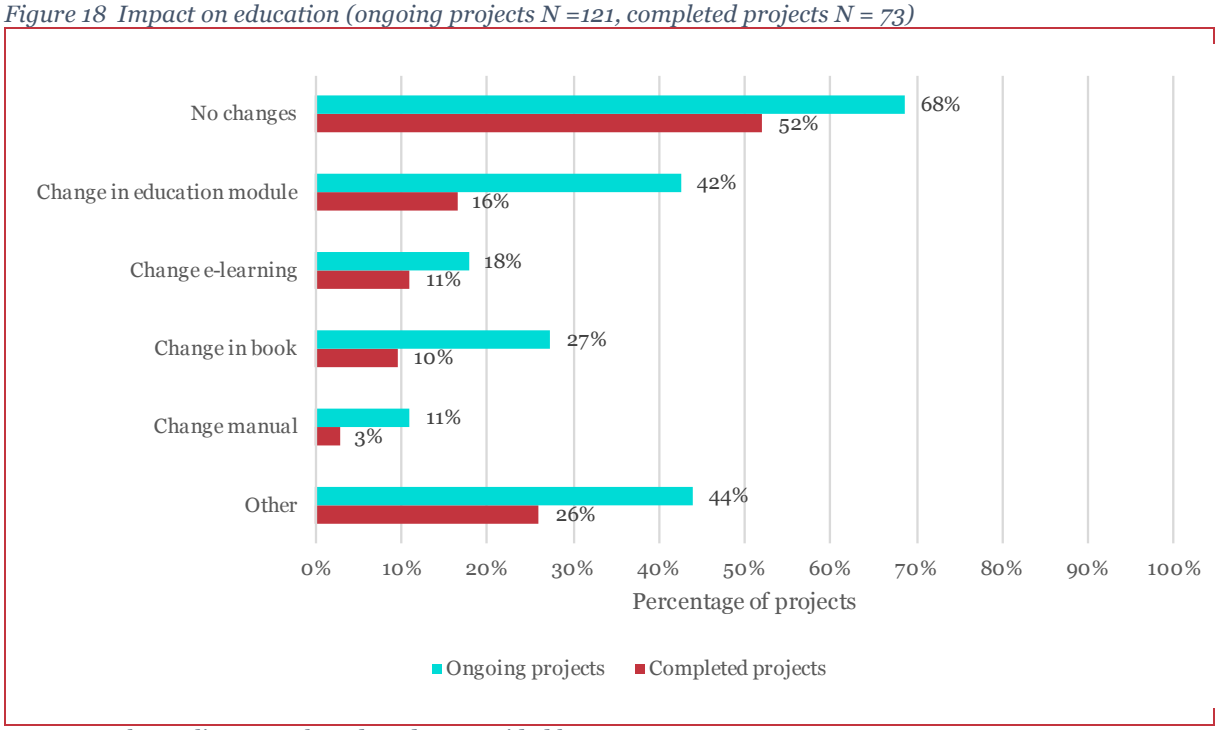
the programme office attempts to track implementation progress also after completion of projects, this data is not captured in the documents reviewed as part of the project results analysis. Therefore, the descriptions provided here may not reflect the current status of translation of project results into practice.

A further time delay between the development of guidelines and their actual adoption by practitioners, means that in the reviewed project documentation no data is available about clinical outcomes beyond the study setting.

5.4.3 Education of healthcare professionals

Survey participants were asked whether their project had resulted in, or was expected to result in, adjustments to the education of healthcare professionals. Participants could indicate if their project had resulted in a changed or new education module, book, manual or e-learning materials (Figure 18). One third of the projects had resulted, or is expected to result, in a change to an education model or other changes. More than half of projects did not result in any changes. Most likely this also was not a project objective.

Figure 18 Impact on education (ongoing projects N =121, completed projects N = 73)



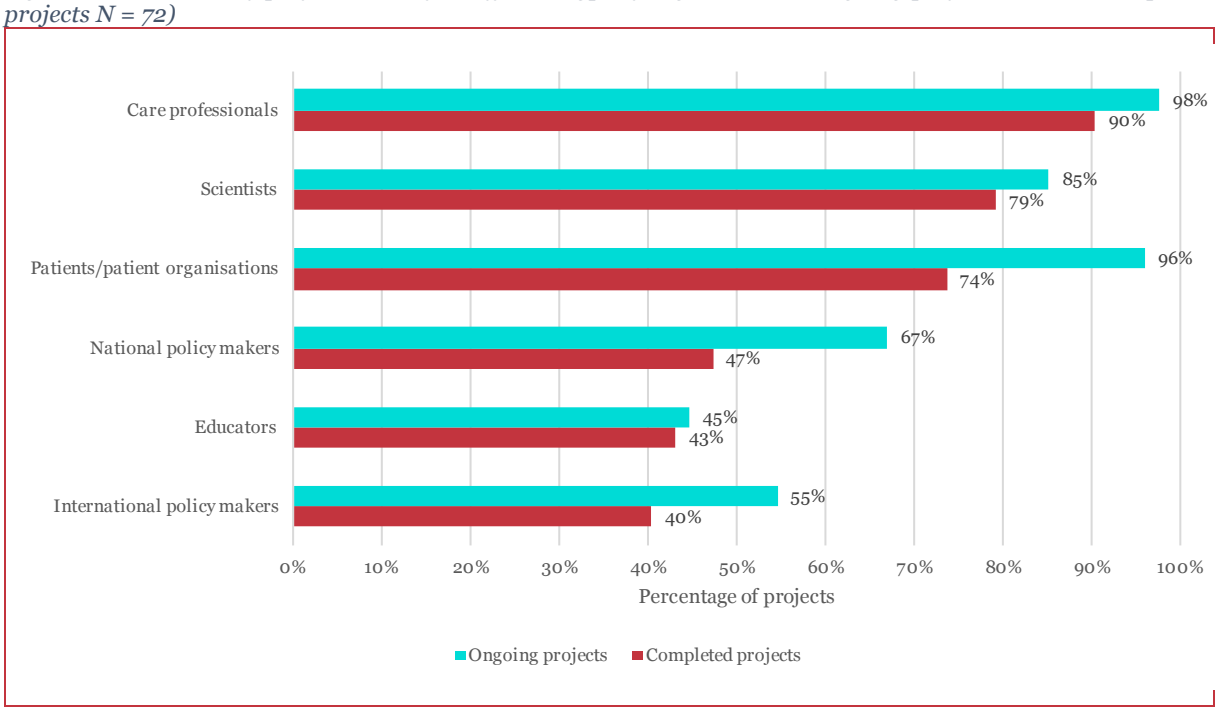
Source: Technopolis Group, based on data provided by ZonMw

Respondents were asked for which parties the results of their project are (expected to be) most relevant (multiple answers possible). Most considered their results relevant to health care professionals, patients and patient organisations and scientists (Figure 19). Half of respondents considered their results relevant to (inter)national policy makers, insurers or educators. The results were considered least often relevant to funds, carers and relatives and businesses.

Not included in the figure are insurers (33% for completed projects and 51% for ongoing projects) , professional associations (28% and 36%), knowledge institutes (25%), citizens, local and regional policy (14% and 32%), carers and relatives (10% and 23%), businesses (11% and 19%), funds (6% and 12%) and the category 'none' (4% of completed projects). The largest difference between completed and ongoing projects is therefore on (expected) relevance for policy (both national, international, local and regional) and for professional associations. Other organisations that were mentioned (in the open

answer box) were: Medical Research and Ethics Committees (MRECs), the Dutch Institute for Rational Use of Medicine (IVM) and ZonMw.

Figure 19 Relevance of project results for different type of organisations (ongoing projects N = 121, completed projects N = 72)



Source: Technopolis Group, based on data provided by ZonMw

5.4.4 Impact on costs

In its final reporting, ZonMw asked researchers to include –where applicable– an estimate of the cost-effectiveness or expected cost impacts of their interventions when implemented nationally. Within the reviewed projects, such data was found for five cases (Table 12).

Table 12 Estimated cost impacts

Project title (number)	**Estimated cost impacts**
Discontinuing inappropriate medication in nursing home residents (DIM-NHR study) (836011019)	A cost analysis suggests the intervention could result in a cost saving of €92 per patient after 12 months. The intervention is applicable to about 140,000 patients per year. This number is expected to increase to 750,000-1,000,000 patients in 2025, which may result in important cost savings
Identifying the right patient to treat, by estimating absolute treatment effect for individual patients based on randomised clinical trial data (836011027)	Treating all patients with intensive lipid-lowering therapy (LLT) resulted in the highest QALY gain (0.14 per patient) against acceptable costs (€17,223/QALY). However, selective benefit-based treatment increases the number of QALYs gained with intensive LLT by statins in individual patients.
The DExamethasone for Cardiac Surgery (DECS) trial: A large but simple trial to quantify the cost-effectiveness of dexamethasone in patients undergoing cardiac surgery. (170885602)	No cost-effectiveness study was done but the lower risk of infections and the reduction of hospital stay suggest that the administration of this inexpensive drug could be a highly cost-effective clinical intervention.
Long term effectiveness of biological use for rheumatoid arthritis in daily clinical practice: analyses on the DREAM registry (836011007)	TNFi mono-therapy is found to be cost-effective compared to combination therapies, but further research is needed to account for health care consumption costs other than medication.

Project title (number)	Estimated cost impacts
Potential optimisation of (Expediency) and Effectiveness of TNF-blockers (152041001)	If 40% of chronic TNFi in RA can be stopped over a 1 year period, there could be a cost saving effect of €200 million within the Netherlands alone.

Technopolis Group 2017, based on documents provided by ZonMw

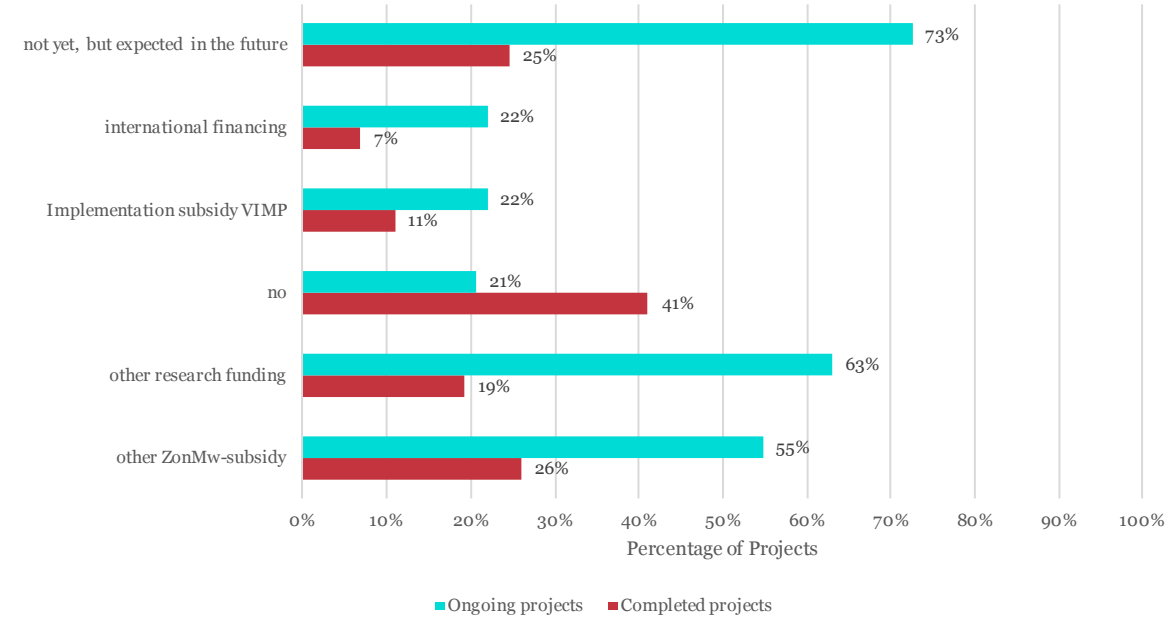
It should be stressed that these cost-effectiveness and cost impact calculations are based on assumptions about, among others, the costs of medications. It is known that these costs can vary. For instance, once medications come off-patent and generic alternatives become available their price can decrease sharply. Such a reduction would, in turn, drastically affect the cost impact. Although the five projects here described provide estimates of the (incremental) cost-effectiveness of a particular course of treatment, only in the study on optimisation of treatment of RA patients with TNFi has this been extrapolated to potential cost savings at a population level, at an estimated cost saving of €200m.

Overall, these projects illustrate that rational pharmacotherapy is often associated with cost savings. Although few data on already realised savings are available, the results described here – when coupled with uptake of the recommended interventions– mean that the programme likely will contribute to cost savings. However, this is not an explicit objective of the programme. Although rational pharmacotherapy can mean reduced use of certain medications, it can equally mean correcting for under-prescription or prescription of more costly medications thereby resulting in increased health care costs but also substantial health gains that outweigh these costs.

5.4.5 Contribution to financing of further research

Survey participants were asked whether their study whether they had been able to attract funding for further research as a result of their project. A high number of project leaders of ongoing projects (73%) indicated they had not yet received further financing, but expected this in the future, in contrast to 25% of project leaders of completed projects. From the project leaders of ongoing projects 63% also (expected) to receive other research funding from, for instance, funds, companies or insurers and 55% of the project leaders from ongoing projects and 26% from completed projects (expected to) receive(d) other funding from ZonMw. Of the project leaders of completed projects, 41% had not been able to attract funding or did not need additional funding for further research as a result of their project.

Figure 20 Financing for further research (ongoing projects N = 121, completed projects N=73)[14]



Source: Technopolis Group based on data provided by ZonMw

5.4.6 Impact on problem awareness

Although not an explicit objective of the programme, various interviewees have indicated that the programme has played a pivotal role in generating greater attention for questions around rational pharmacotherapy. It has done so not only through the projects, where non-traditional parties have been involved in the research, but also through the representation in the GGG-council and the programme committees. The public attention for the programme, catalysed also by the GGG conference, and the visible political commitment have further helped engender the involvement of a wide range of stakeholders. As one interviewee said:

> *An added effect is that important parties involved in the development and prescription of drugs are now sitting together at the table. Rational pharmacotherapy has become an established concept that everyone understands, that is very important. The programme, the meetings and certainly also the GGG conferences – which are enormous happenings– contribute to that.*

[14] A VIMP stands for Dissemination and Implementation Impulse (Dutch: Verspreidings- en implementatie Impuls) and is an additional grant that can be awarded to projects that have obtained promising results (ZonMw, 2017)

6 Conclusions

The final chapter of this report brings together the main evaluation findings and places these in context to arrive at a set of conclusions. Conform the evaluation assignment, the formulation of recommendations has been entrusted to the external evaluation committee and will be presented by the committee separately.

6.1 Programme management and organisation

The GGG-programme has a clear organisational structure where different type of bodies have distinct responsibilities. The programme office, responsible for overall programme coordination, is widely viewed as committed, professional, and knowledgeable. In addition to its day-to-day coordination tasks, the office plays an important role in continuously shaping the programme by seeking input from, and collaborating with new sets of stakeholders. It has done so, amongst other things, by successfully attracting third party funding thereby allowing for the launch of new programme modalities. Despite its relative large staff, the programme coordinators indicate there is insufficient capacity to fulfil all their ambitions. This suggests that either additional capacity is needed or that the programme office needs to set clear priorities.

The selection of projects has been entrusted to programme committees that are composed to account for the wide range of expertise needed. It has at times proven challenging to populate the committees with knowledgeable, yet sufficiently independent experts, but currently there appears to be adequate capacity. The programme office and committees are supported in their responsibilities by the programme council, which provides valued high-level steering to the programme. It has been noted that the council could take a more pro-active role in liaising between the programme and other stakeholders.

In recent years, patient panels have been involved in the proposal assessment procedures but the programme is still exploring how their role can be optimised.

Overall the managerial structure of the programme appears to function well and is well-suited to the objectives of the programme.

6.2 Programme structure and portfolio

Within the programme several thematic priorities have been defined: efficiency and effectiveness, tailored pharmacotherapy, other indications, adherence and polypharmacy, implementation and infrastructure. These priorities are addressed through projects that are funded through different funding modalities.

Initially, the programme was structured around two modalities, the Open Round and Registry modalities. Several modalities have since been added in response to identified challenges, but the Open Round remains the principal modality of the programme. Up till May 2017, €34.9m (76% of total funding granted) has been allocated to a total of 104 projects in the Open Round.

Within the Registry modality, designed to support sustainable initiatives for the development of patient registries (corresponding to the priority on 'infrastructure'), thus far a total of €4.2m (10%) has been awarded to 16 registry projects. In 2016 and 2017 no calls were issued. Discussions are ongoing about the positioning of this modality within the rational pharmacotherapy landscape.

Responding to concerns about the gap between generation of evidence through research and implementation and uptake of evidence in practice, in 2014 the STIP modality was launched. Up till May 2017, a total of €2.1m (5%) has been awarded to 19 implementation projects. In June 2017, it was decided to suspend the STIP modality for a maximum of one year, to allow a reassessment of how implementation into practice can be made more effective.

The Large Multicentre Trials modality was launched in 2015 to facilitate projects of over €1m. So far, three projects have been funded at a total of €4.2m (9%). The Personalised Medicine and Rediscovery

modules were only recently added to the programme and have not been included in detail in this evaluation.

Together, the four modalities discussed cover the entire range of thematic priorities. However, the coverage is uneven. Out of all 142 projects in the four modalities analysed, 51 projects fell within the thematic area of efficiency & effectiveness. By contrast, only nine projects were awarded in the area adherence & polypharmacy. Although interviewees have postulated several explanations, this evaluation was not designed to identify the root causes. If adherence and polypharmacy are considered a continued priority within the programme, a further problem analysis will be needed to identify the main barriers and inform corrective actions.

The relative distribution of projects over the four research priorities is largely dependent on the relevance and quality of applications in each of those areas. The programme therefore has limited direct control over this, although it can provide additional support to researchers in certain areas or issue specific calls. By comparison, the GGG-council can exert greater influence over the relative weight assigned to the priorities of implementation and infrastructure, by adjusting the amount of funding available for the corresponding modalities (i.e. STIP and Registries).

6.2.1 Application and selection processes

Throughout the years, the average success rate for applications (starting from initial project ideas) has been around 14%, with some variation across funding modalities. This is consistent with many other research funding programmes, both within ZonMw and elsewhere. The success rate increases to 35% for full proposals.

From the perspective of programme management, the two-step application process has the advantage that low quality project ideas can be eliminated at an earlier stage, thus reducing the burden on proposal reviewers. On the other hand, lowering the initial application threshold may greatly increase the number of applications, intensifying both the work of the programme committees and of the project office. Narrowing the scope of calls would likely limit the number of proposals received. This would increase applicants' chances of success with the added benefit of reducing the administrative burden. Yet, the openness of the calls is valued by many who see few alternative funding options and who fear that narrowing the scope of calls would mean that potentially relevant project ideas would no longer be able to attract funding.

It is worth noting that, despite the high number of rejections, the programme supports an extensive project portfolio. Effective management of this entails considerable investment of resources, as attested to by the workload perceived by the programme office. It is worth further reviewing whether the current programme set-up is optimal, taking into account future strategic decisions.

6.3 Programme outputs

Although the majority of projects is still ongoing, the programme has already generated a substantial research output in the form of scientific publications and presentations. Based on self-reporting by researchers, there is an expected output of seven publications per project on average, although methodological limitations mean this number is likely to be somewhat overstated. Thus far, over 900 articles have been published that have been linked to research supported by the programme.

In pursuit of the strategic goal to "strengthening the infrastructure in which relevant questions around rational pharmacotherapy can be answered", the programme has supported the development of a number of patient registries. Of these three are operational, albeit at a limited scale. An additional 13 are in various stages of development.

The programme has been an important catalyst in "building and maintaining a network of parties that are involved with pharmacotherapeutic care and rational pharmacotherapy", another of its strategic goals. For one, it has fostered greater collaboration within the academic community. Perhaps more importantly, though, it has also managed to engage a variety of parties that have not traditionally been involved in research projects of this kind. Nonetheless, there are indications that the programme could

still benefit from greater engagement with, for instance, practitioners, professional medical associations and regulatory bodies.

6.4 Programme results and (potential for) impact

Amongst the programme's strategic goals, the first three are most directly linked to the support given for research activities:

- Facilitate pharmacotherapy-related research to provide evidence to substantiate the 'pharmaceutical care' sections of guidelines and/or care standards.
- Answering pharmacotherapy related research questions that result in the improvement of quality of care in practice, where there is a need.
- Address pharmacotherapy-related research questions that are relevant to the work of decision-making bodies, including the Medicines Evaluation Board (in Dutch: CBG) and the National Health Care Institute (in Dutch: ZiN).

As most of the research activities are still ongoing, or have only recently been completed, results are either not yet available or have not yet had time to be widely shared. It is therefore too soon to clearly tell what the contribution of the programme will have been to each of these goals. Still, analysis of a selection of projects drawn from the project portfolio already highlights a wide range of results that can contribute to improvements in clinical practice. Many of the results identified in this evaluation will have implications for the efficiency and effectiveness of pharmacotherapy when put into practice. We also found numerous examples of projects that may result in reduction of medication, either by addressing unnecessary polypharmacy or by enabling treatment that is tailored to the individual patient.

For the most part, though, the identified results signal the *potential* of the programme to contribute to more efficient, safer and effective use of available medication. One should herein bear in mind the considerable time lag between completion of research projects, translation of knowledge and subsequent adoption into practice. For instance, the development (or revision) of clinical guidelines was said to frequently take three to four years from the moment that research findings become accessible in the form of, for instance, scientific articles. Together with the time needed for publishing results in academic journals, this means that easily five years may pass before research findings find their way into clinical practice. Across the whole of the programme it is therefore premature to draw conclusions about contributions to the overarching programme objectives.

Similarly, the impact of the programme on health care costs cannot yet be established. Initial estimates of cost impacts for various completed projects suggest that, if the proposed interventions are adopted nationally, the programme could indeed result in large cost savings. If these estimates will be validated in practice, the programme will have paid for itself many times over. However, this is contingent on many different parameters and thus for now remains largely hypothetical.

6.5 Programme challenges

The GGG programme was created in response to a clear societal need for research to better understand and promote rational pharmacotherapy in practice. Since its creation, the programme has grown into an important funding source for this type of research and has put the topic on the agenda of a wide range of parties. Results achieved to date also suggest that the programme has a great deal of potential. Researchers value the programme as an important source of funding in an area where there are few alternative funding options. Nonetheless, the evaluators identified several challenges facing the programme.

6.5.1 Approach to programming

First, throughout, the programme has been characterised by a willingness to learn and a flexibility to respond to challenges. The addition of new modalities and fine-tuning of existing modalities over the years is testament to this. Indeed, many have stressed that the complexity of the rational pharmacotherapy topic requires such responsiveness and have lauded the programme for it. The

evaluators share this sentiment, but also point out the risk of the programme becoming a mix of individual modalities rather than a coherent programme, if the programme structure is not given sufficient time to stabilise.

Coherence is further challenged by the way in which projects are selected. At the moment, most of the programming is done bottom-up. In the Open Round, in particular, applications are not bound to specific themes or disease areas. Consequently, the project portfolio has become very diverse and it is not immediately apparent if, and how, the programme promotes synergy between projects. Such synergy is particularly important in connection to the programme's stated objectives of 'facilitating research to substantiate guidelines and care standards', and 'answer questions that are relevant to decision-making bodies'. In this light, it is worth emphasising that, although each project is selected – in part – for its relevance, individual studies rarely drive these kinds of changes to practice. Rather, this requires a sufficient body of evidence, with projects building upon and linking to similarly focussed research, conducted both nationally and internationally. The programme itself underscores the importance of this in its strategic goal of 'staying up-to-date with relevant developments around rational pharmacotherapy and finding connections where necessary'.

Last, although the composition of the programme committees and the GGG-council is designed to help connect the programme to its stakeholders, several interviewees still feel that the programme should more closely consult the (medical and pharmaceutical) field in the determination of its programmatic priorities and articulation of selection criteria. The knowledge agendas of the medical professional organisations, in particular, were repeatedly mentioned as an important source of input to be taken into account.

6.5.2 Implementation challenges

Despite persistent efforts to stimulate the implementation of results in practice, such as the addition of the STIP modality, a number of interviewees closely involved with the programme have signalled that implementation remains a challenge. It has been suggested part of the problem lies in the fact that practitioners, such as health care providers (across the care spectrum), pharmacists or nurses, have not been sufficiently involved in the programme. Their lack of connection can create a translation gap if researchers are not sufficiently connected to the parties that who can drive implementation and uptake.

In their assessment of proposals, the programme committees already pay considerably attention to proposed involvement of stakeholders and have been known to encourage researchers to involve relevant parties. However, there is no formal requirement on project leaders to take responsibility for implementation. Such a requirement would even be unlikely to be successful, as oftentimes researchers do not have the necessary expertise, nor the time to do so. On the part of ZonMw, once research projects are satisfactorily completed, the formal involvement of the programme office ends and final payments are made. After this, neither party has a contractual obligation for ensuring or supporting implementation. Moreover, as a research funding organisation, ensuring implementation is not part of the mandate given to ZonMw. Nonetheless, the mission of the GGG programme has been ambitiously stated as "to ensure that (existing) medication is deployed in a more effective, safe and efficient manner, to enhance the quality of pharmacotherapeutic care for patients and to improve cost-efficiency in care and/or for society". This mission obviously necessitates implementation. This therefore raises the question of where the responsibility for implementation should rest and what the programme can do to further stimulate this, beyond the tools it already has at its disposal.

Appendix A Evaluation questions and methodology (in Dutch)

The following table presents the underlying evaluation questions in relation to the methodology.

Evaluatievraag	Methoden
Procesevaluatie	
Op welke wijze is het GGG-programma ingericht om haar doelstellingen te realiseren?	
Wat is de rol van de verschillende programmacommissies en welke bijdragen leveren zij?	
Welke rol speelt het programmasecretariaat? Hoe effectief voert het deze rol uit?	
Hoeveel aanvragen zijn ingediend? (Naar programma (ronde)/ activiteit/organisatie) – Hoeveel aanvragen zijn gehonoreerd? (Naar programma (ronde)/ activiteit/organisatie)	
Is de toegankelijkheid van het programma voldoende geborgd? – Is er spreiding van projecten over o.a. de verschillende UMCs en zorginstellingen? – Zijn de voorwaarden belemmerend voor bepaalde groepen?	
Wat is het aandeel van andere (publieke en private) partijen per programma/project? – Waarom doen relevante partijen al dan niet mee? – Zijn verwachtingen van deelnemende partijen uitgekomen?	
Is er sinds 2012 noodzaak geweest om programma's bij te sturen? – Zo ja, waarom en hoe is dit uitgevoerd? – In hoeverre zijn activiteiten ongeschikt bevonden tijdens de looptijd van het GGG-programma of werden activiteiten gemist?	
Wat is ondernomen om het huidige GGG-programma uit te laten groeien tot dé structurele financieringsbron van GGG-onderzoek in Nederland?	
Op welke wijze worden relevante (inter)nationale ontwikkelingen op het gebied van goed gebruik geneesmiddelen gevolgd en betrokken in het programma? – Zijn er (inter)nationale ontwikkelingen waar aansluiting is gezocht en ook gevonden?	
Resultaatevaluatie	
Opbrengsten in de vorm van outputs	
Op welke wijze heeft het programma bijgedragen aan de versterking van de infrastructuur waarin vragen op het gebied van rationele farmacotherapie adequaat beantwoord kunnen worden (zowel voor interventieonderzoek als observationeel onderzoek)? – In welke mate heeft het programma bijgedragen aan het vormen of versterken van netwerken van partijen die betrokken zijn bij rationele farmacotherapie en farmaceutische zorg? – Hoe worden de netwerken onderhouden?	
In welke mate hebben de gefinancierde projecten geleid tot nieuwe of verbeterde inzichten, of valt dit nog te verwachten in de nabije toekomst? Wat zijn de outputs geweest in, onder meer: – Publicaties (e.g. wetenschappelijke artikelen, boeken, theses, nieuwsberichten) – Presentaties (e.g. op vakconferenties, bij patiëntenverenigingen) – Opgeleide wetenschappers (e.g. aantal promoties, post-docs)	

In welke mate heeft het programma bijgedragen aan het opzetten of uitbreiden van patiëntregistraties? – In hoeverre creëren deze meerwaarde voor efficiënte en veilige inzet van geneesmiddelen?	
Opbrengsten in de vorm van outcomes	
In hoeverre hebben de resultaten van het programma bijgedragen aan, onder meer: – De ontwikkeling van nieuwe richtlijnen en/of zorgstandaarden – Product- en zorginnovaties m.b.t. geneesmiddelengebruik (bijv. Verbeterde etikettering) – Nieuwe productregistraties (o.a. vanuit de Rediscovery Ronde)	
In hoeverre zijn resultaten uit het programma relevant gebleken voor het werk van besluitvormende instanties, zoals het Zorginstituut Nederland (ZiN) en het College ter Beoordeling van Geneesmiddelen (CBG)?	
Zijn er 'bijvangsten' van de projecten en het GGG-programma als geheel? (Onbedoelde bijkomende effecten, zowel positief als negatief)?	
Opbrengsten in de vorm van impact	
In hoeverre worden, als gevolg van het GGG-programma, geneesmiddelen effectiever, veiliger en doelmatiger ingezet? – Zijn er voorbeelden (cases) waaruit de invloed van het GGG-programma blijkt op het goed gebruik van geneesmiddelen blijkt?	
In hoeverre is er sprake van gerealiseerde of te verwachten gezondheidswinst en/of verbeterde kosteneffectiviteit?	
Op welke terreinen zijn beoogde resultaten niet gehaald? – In welke mate worden knelpunten bij de implementatie van dankzij het programma opgedane kennis systematisch geïdentificeerd en worden relevante oplossingsrichtingen gezocht?	
Verbeterpunten voor vervolgprogramma's	
Welke problemen zijn projectleiders, programmacoördinatoren en (voorzitters van) programmacommissies tegen gekomen? Hoe kunnen deze opgelost worden?	
Wat waren kritische succes- en faalfactoren voor de verschillende programmaonderdelen en het GGG-programma als geheel?	
Welke verbeterpunten zijn te benoemen?	
Welke aanbevelingen kunnen geformuleerd worden voor de ZonMw programmering?	
 = Analyse programma- en projectdocumentatie  = Analyse projectportfolio en surveydata  = Interviews	

Appendix B Members Independent Evaluation Committee

1.	prof.dr. H.G.M. (Bert) Leufkens, chair (chairman of the Medicines Evaluation Board, until 1 Aug 2017. Professor of pharmaceutical sciences Utrecht University
2.	dr. E. (Eric) Roos (chairman of the board of the Parkinson Association)
3.	prof.dr. M.Y. (Marjolein) Berger (professor primary care UMCG)
4.	drs. M.M. (Mathieu) Tjoeng (hospital pharmacist, former chairman of the NVZA)
5.	dr. M. (Martin) Smalbrugge (elderly care physician VUmc)
6.	prof.dr. W.B.F. (Werner) Brouwer (professor Health Economics iBMG/Erasmus Universiteit)
7.	drs. R.J.W.M. (Ruud) Coolen van Brakel (director IVM)
8.	drs. P. (Paul) Korte (Janssen-Cilag BV, chairman VIG)
9.	drs. J.W.M.W. (Joël) Gijzen (CZ Health Insurer)
10.	prof.dr. P.B.A.M. (Paul) Smits (professor Pharmacology Radboud UMC) *until May 2017*
11.	dr. M. E. (Elske) van den Akker-van Marle, secretary (health economist, LUMC)

Appendix C List of interviewees

C.1 Stakeholder interviews

Maaike Alderliesten	KWF Kankerbestrijding
Douwe Breimer	Universiteit Leiden
Jako Burgers	Nederlands Huisartsen Genootschap
Saco de Visser	ZonMw
Martin Favié	BOGIN - belangen organisatie voor biosimilars en generieke geneesmiddelenindustrie
Christine Gispen-de Wied	College ter Beoordeling van Geneesmiddelen
Gerben Klein Nulent	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
Ingrid Lether	Reumafonds
Ingeborg Lijst	Zorg en zekerheid
Martin Potjens	Zorgverzekeraars Nederland
Gerard Schouw	Vereniging Innovatieve Geneesmiddelen
Klaartje Spijkers	Patiëntenfederatie Nederland
Ghislaine Steenberghe	Zorg en zekerheid
Linda ten Boden	Zorg en zekerheid
Teus van Barneveld	Federatie Medisch Specialisten
Martin van de Graaff	Zorginstituut Nederland
Linda van Saase	Zorginstituut Nederland
Benien Vingerhoed-van Aken	ZonMw

C.2 Interviews with (non-) successful applicants

Petra Denig	UMC Groningen
Carla Hollak	Academisch Medisch Centrum
Tim Janssen	VieCuri
Catherijne Knibbe	St. Antonius Ziekenhuis
Mathieu van der Jagt	Erasmus MC
Anneke van der Veen	GGNet
Jaap van Dissel	LUMC
Tom van Mierlo	VUMC
Saskia Vorstenbosch	Lareb
Michiel Bots	UMC Utrecht
Walter van den Bergh	UMC Groningen

Appendix D Participants Group Interviews

GGG-council

Dick Dees

Martin Favie

Gerben Klein Nulent

Marian Mens

Gerard Schouw

Jako Burgers

Fred Schobben

Marcel Daniels

Programme Committee (Large Multicentre Trials , Open Round, Rediscovery)

Thea van Asselt

Anton de Boer

Daphne Bloemkolk

Marcel Bouvy

Mariette Driessens

Manuela Joore

Henriette van der Horst*

Ben van der Zeijst*

*These members were interviewed individually because of technical problems at the time of the group interview

Committee Personalised Medicine

Pauline Evers

Eduard Klasen

Marja Kuijpers

Sabine Linn

Gerrit Meijer

Committee Patient Registries

Marcel Daniels

Erik Flikkenschild

Jacob Hofdijk

Stephanie Weinreich

STIP Committee

Denhard de Smit

Johanna Haanstra

Yvonne Huisman

Tom Kleijn

Anne-Marie Prins-Jacobs

Joris Uges

Jaap van der Laan

Toon Voorham

Joost Zaat

Frans Zitman

Appendix F Methodology programme results

A result analysis was done using two main methodologies. First, we analysed responses to a survey developed and administered by the programme office that collected (self-reported) data on outputs, outcomes and impacts of the projects. Second, we reviewed available project documentation (proposals, progress reports and final reports) for a selection of projects. The two methodologies are described in more detail below.

F.1 Project survey

Two versions of the survey were developed: one for project leaders of ongoing projects and one for project leaders of completed projects. The survey was sent to 251 project leaders. The response rate of the survey was 87% for ongoing projects and 75% for completed projects. Analysis consisted of:

- Removal of duplicates from the data (due to resubmission of incomplete responses).
- Restructuring the data for analysis.
- Translation of the response categories to English.
- Quantitative and qualitative analysis of responses.

A total of 199 responses were included in the analysis, of which 76 were for completed and 123 for ongoing projects. These are projects from the Open Round, STIP, Patient Registries and Top Down modalities, but also from the predecessor programmes that were put under the umbrella of the programme (Table 13).

The total number of responses (projects) per modality is given below. However, since sometimes a project leader did not answer a specific question, the total number of responses per question (N) is provided with each graph.

Table 13 Number of projects included in the analysis per modality

7	Open Round	STIP	Patient Registries	Top Down	Predecessor programmes
Completed projects	5	3	0	2	66
Ongoing projects	70	11	11	1	30

Although the survey responses provide valuable insights into the entire chain from activities to impacts, there are clear data limitations. First, the survey data rely on self-reporting, which introduces significant uncertainty about the accuracy of data. In particular data on outputs are likely to be inaccurate and incomplete. For instance, there may be inadvertent double counting of publications, when project leaders have been involved in several, complementary studies. Also, publications may have been counted that are related to research funded through the programme, but that are not necessarily a direct output from it. Triangulation with data available from the programme bureau would not solve this issue, as this is known to be incomplete. Once projects have been completed, investigators often no longer provide updated information to the programme office.

F.2 Selected project analysis

Within the scope of this evaluation it was not feasible to produce a complete overview of all realised and potential outcomes to date. Therefore, a selection of projects was made that can be considered representative of the entire portfolio. The selection was made on several criteria to achieve appropriate distribution over:

- Programme modality

- Thematic priority
- Funding amount (stratified)[15]
- Type of lead organisation

As this analysis focused on outcomes and impacts achieved to date, projects were only considered eligible if at least 75% of the project duration[16] had passed. Only for projects in the more recently initiated Large Multicentre Trials modality this was not a requirement. Several projects that were subsequently found to have been terminated or significantly delayed were removed from the initial sample – as their added value in the context of a results evaluation was limited – and substituted with projects with similar characteristics. At the request of the programme office and the independent evaluation committee, the sample included a limited number of projects drawn from a list of projects from the predecessor programmes identified by the programme office as 'high impact' projects. As a result, the sample has a degree of positive selection bias. However, as the result analysis is not purely intended as a representative reflection of achieved results, but is also meant to demonstrate the potential for impact, their inclusion is considered justified.

Available project documentation was reviewed for 26 selected projects (Appendix G). To further deepen our understanding, interviews were conducted with the principle investigators of 9 of these projects.

[15] Stratification by funding amount was mainly done for projects funded in the Open Round, where there was the largest variation in amount of funding awarded.

[16] As based on the initial project duration mentioned in the project proposals. Project extensions and delays due to late initiation were thus not accounted for.

Appendix G Project results table

Title	Design (method)[17]	Description	Results
Efficiency & Effectiveness			
How appropriate is the increasing long term use of methylphenidate? A practice audit and placebo controlled discontinuation trial. (836011014, Open Round)	**Experimental** RCT	Over the last decade, there has been a rapid and tremendous increase in the diagnosis of ADHD and in the use of medication treatments for ADHD such as methylphenidate. It is unclear whether children are being over-diagnosed. There is also a lack of research on the long-term use of methylphenidate to support current prescription practices. OBJECTIVES: 1. To study current long-term prescription practices and policies of methylphenidate in daily clinical practice by conducting a large scale audit. 2. To investigate the effectiveness of treatment continuation with methylphenidate beyond two years of treatment. Based on study outcomes an implementation plan will be made on the improvement of the long-term prescription practice of methylphenidate.	**Ongoing** No results available yet
The DExamethasone for Cardiac Surgery (DECS) trial: A large but simple trial to quantify the cost-effectiveness of dexamethasone in patients undergoing cardiac surgery. (170885602, DO Farmaco)	**Experimental** RCT	Cardiac surgery is among the most commonly performed surgical procedures, with over 1 million patients being operated every year. These operations usually require the use of a heart-lung machine, but this is not without side-effects. The contact of the blood with the heart-lung machine leads to a profound inflammatory response, which may contribute to the risk of postoperative complications. The drug dexamethasone (a corticosteroid) is used in many European hospitals but not in most north-American ones. This is due to the adverse reactions in prolonged use. OBJECTIVES: To see the postoperative effects of dexamethasone on the patient.	**Completed:** Patients who received dexamethasone had a slightly better postoperative course than those who received the placebo. They required a shorter stay in the intensive care unit and could be discharged one day earlier from the hospital. Moreover, they had fewer infectious complications. There was a strong age effect; patients younger than 75 years had a strong benefit of dexamethasone. Concurrently, the small group of patients over 80 years who got administered the drug had an increased risk of adverse effects. The lower risk of infections and

[17] The design and method listed here are only those of the component of the study that is used to measure effects on the primary outcome. In many cases, additional methods are used, for instance, in development of the intervention, for pilot testing, for collection of qualitative data on user experiences, or to estimate cost-effectiveness.

Title	Design (method)[17]	Description	Results
			the reduction of hospital stay suggest that the administration of this inexpensive drug could be a highly cost-effective clinical intervention.
Paracetamol or NSAIDs in acute musculoskeletal syndromes (The PanAm Study) (836011015, Open Round)	**Experimental** RCT	At the emergency department and in general practices, pain in patients with traumatic musculoskeletal injuries is often treated with paracetamol or Non-Steroidal Anti-Inflammatory (NSAID's). There is no convincing proof in the literature that NSAID's are more effective than either paracetamol or a combination of the two. Paracetamol is more desirable than NSAIDs due to the adverse effects, especially in elderly patients. OBJECTIVES: To compare analgesic effectiveness and safety of an NSAID or paracetamol or a combination of both in treating adult patients presenting to the emergency department or in general practice with acute musculoskeletal syndromes. Primary outcome is pain and secondary outcomes are adverse events, patient satisfaction with pain relief and cost-effectiveness.	**Completed:** The PanAM Study shows that in adult patients with minor acute musculoskeletal injury, paracetamol works as well as diclofenac or paracetamol with diclofenac. There was no difference in decrease of pain scores in the acute phase between the three intervention groups, in rest as well as with movement of the extremity involved. During three consecutive days after discharge, there was no difference between paracetamol, diclofenac or the combination of both drugs in decrease of pain as well (in rest and with movement). No difference was found in side effects. However, all patients received stomach protection, besides the study medication. Therefore, the study results are not a reliable reflection of daily clinical practice.
Optimizing DMARD therapy for primary Sjogren's syndrome (836021005, Open Round)	**Experimental** RCT	Primary Sjogren's syndrome (pSS) is characterized by chronic inflammation of the exocrine glands, resulting in severe dryness of eyes and mouth. Autoantibody production by B cells in pSS is associated with increased disease activity and B cell lymphoma (in 5-10%). The high costs (€8000 per year per patient) of B cell depletion are a major drawback for large-scale	**Ongoing:** *In vitro* studies found that HCQ and LEF robustly inhibit both T- and B-cell proliferation, cytokine- and immunoglobulin production. Moreover, the combination of HCQ and LEF additively inhibited these cellular processes.

Title	Design (method)[17]	Description	Results
		implementation of this therapy, increasing the need for reasonable alternatives, currently not available. OBJECTIVES: To carry out a randomized placebo-controlled clinical trial to study the effects of Hydroxychloroquine and Leflunomide combination therapy in patients with primary Sjogren's syndrome (pSS). If successful the therapy would cost a significant amount less (€ 607 per year per patient). Additionally, detailed immunomonitoring in the study will aid to predict therapy responsiveness and unravel pathways that confer therapy resistance.	These findings indicate the potential surplus value of combination therapy with HCQ and LEF for patients with pSS. At the time of last reporting patient enrolment into the RCT was ongoing.
Reducing vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukaemia by one-hour infusions instead of bolus injections. (836021006, Open Round)	**Experimental** RCT	Vincristine (VCR) is a commonly used chemotherapeutic drug in the treatment of paediatric acute lymphoblastic leukaemia (ALL). The main dose-limiting side effect of VCR is peripheral neuropathy (PNP). PNP is often seen in the form of weakness of lower limbs, areflexia, neuropathic pain, and/or sensory loss. Also constipation, a neuropathy of the autonomic nervous system, is a common phenomenon. The quality of life of children who suffer from VCR-induced PNP is severely affected. There is a lack of information regarding the optimal therapeutic dosing and method of administration of VCR for children with cancer. OBJECTIVES: To investigate whether the administration of VCR in children with ALL by one-hour infusions leads to less PNP compared to bolus injections. Furthermore, QoL, medical costs and therapeutic effectiveness associated with both administration methods will be evaluated. Finally, other factors will also be tested on their influence on the degree of PNP.	**Ongoing:** Thus far, an online study database has been created.
Potential optimisation of (Expediency) and Effectiveness of TNF-blockers (152041001, DO Farmaco)	**Experimental** RCT (The initial study was broken off. It was continued as a cohort study (observational))	For the treatment of Rheumatoid Arthritis (RA) it is common practice to use TNF inhibitors (TNFi) if there is insufficient effect of the csDMARDs. Once the RA is in remission the treatment usually continues for a long period of time, as RA is a chronic disease. There are two downsides to this prolonged treatment: 1) long term safety and 2) high costs for the Dutch	**Completed:** In the group that stopped treatment of TNFi, 51% had an exacerbation within a year versus 18% in the control group. The hazard ratio for an exacerbation of RA is 3.5 and the average disease score was significantly higher in the experimental

Title	Design (method)[17]	Description	Results
		health care budget. OBJECTIVES: To see whether it is possible to stop patient treatment with TNFis when the RA has gone into remission for a period of time.	group. It is estimated that, if 40% of chronic TNFi in RA can be stopped over a 1 year period, there could be a cost saving effect of €200 million.
CHolinEsterase inhibitors to slow progression of Visual hALlucinations in Parkinson's disease: a multi-centre placebo-controlled trial (CHEVAL) (836011029, Open Round)	**Experimental** RCT	Visual hallucinations (VH) are the most common non-motor symptoms in Parkinson's Disease (PD). In the disease development of PD, minor VH precede major VH and PD associated psychosis (PDP). As of now there are no guidelines for the treatment of minor VH, but cholinesterase inhibitors (ChEl) might be a well-tolerated alternative for the early treatment of minor VH to delay the progression to PDP. OBJECTIVES: To investigate whether early treatment with ChEI delays the progression of minor VH to major VH without insight or PDP. Additional outcome measures were motor control, psychotic symptoms, cognitive impairment, adverse events, quality of life, caregiver burden and care use. The cost-effectiveness of early chronic treatment of VH with ChEI is also assessed.	**Ongoing:** No results available yet
Long term effectiveness of biological use for rheumatoid arthritis in daily clinical practice: analyses on the DREAM registry (836011007, Open Round)	**Observational** Retrospective cohort study and case control studies	The cause of rheumatoid arthritis (RA) is unknown but currently it is being treated using tumour necrosis factor alpha inhibitors (TNFi). Experience with long-term use of these TNFis has raised new questions on their use. Literature has shown that antibodies may form against the antibodies of two TNFi's but this has never been proven for etanercept. The long-term use of 3 prominently used drugs (infliximab, etanercept and abatacept) is compared. Another RA treatment, called MTX, is also tested. OBJECTIVES: Three main analysis were proposed: 1. Short and long-term use of 3 TNF inhibitors was tested to re-evaluate their effectiveness and drug survival. 2. Furthermore, the synergistic effects of MTX with TNFi's was tested and MTX's assumed inhibition on the formation of anti-bodies against TNFi. 3. The possibility of cycling the three TNFis, for instance when one TNFi has failed, was tested.	**Completed:** 1. Etanercept or adalimumab have better long-term effectiveness than infliximab. Moreover, etanercept users are more adherent to their medication and etanercept is thus the preferred TNFi. Decision trees for the use of TNFi therapies were made that will help rheumatologists and RA patients in treatment decision making. 2. Use of MTX as co-medication is recommended as it is more effective than TNFi mono-therapy. When there are contraindications for the use of MTX, the other DMARD are recommended. There was a larger than expected difference between mono

Title	Design (method)[17]	Description	Results
		For all analyses the DREAM registry was used.	and combination therapy. However, this was attributed to a higher percentage of mono TNFi users who stopped their treatment and a 1-2 month delay until the start of a second biological agent. 3. There was insufficient data in the DREAM database to reliably answer this question.
Quality of prescribing: patient specific indicators that predict better outcomes in diabetes patients (836021007, Open Round)	**Observational** Cohort study	The current Dutch quality indicator set for diabetes care lacks good indicators for measuring quality of medication treatment. OBJECTIVES: To develop a set of valid indicators to be used for evaluating and improving chronic medication treatment in Type 2 diabetes patients. These novel prescribing quality indicators should (1) capture the quality of chronic treatment over time, (2) take into account differentiation for patient characteristics, (3) predict better patient outcomes, and (4) be measurable using routinely collected data from primary care.	**Ongoing:** An initial list of 32 potential indicators has been assessed by an expert panel. From this, a revised list of 22 indicators was made and revised again by the same panel. A final list of 20 indicators is now being applied using two available databases with routinely collected data from general practices.
Pharmacokinetics and Pharmacodynamics of Medication in Asphyxiated New-borns During Controlled Hypothermia. PharmaCool National Multicentre Study (113201001, PMK)	**Observational** Prospective cohort study	Since 2009, all 10 Neonatal Intensive Care Units (NICUs) in the Netherlands have adopted controlled hypothermia as the standard of care in neuroprotection for perinatal asphyxia cases. Unfortunately, the potential benefits of therapeutic hypothermia may be offset by ineffective or harmful effects of life saving medications due to the unknown PK/PD of these drugs during hypothermia. OBJECTIVES: To develop an evidence based effective and "safe" dosing regimen for commonly used lifesaving medications used in the treatment of asphyxiated, critically ill new-borns, undergoing therapeutic hypothermia. To this aim the PK/PD properties of three groups of drugs (antibiotics, analgesics, sedative & anti-epileptics) will be	**Completed:** The study found decreased clearance during hypothermia of Gentamycin, Amoxycillin, Lidocaine, and Morphine, resulting in new suggested dosing regimens. More drugs are still being analysed: midazolam, makikacin, penicillin and cephalosporin. This study has also led to improved analysis methods for plasma drug levels in very small blood sample amounts.

Title	Design (method)[17]	Description	Results
		investigated in a prospective cohort of patients.	
Adherence & Polypharmacy			
Personal Antipsychotic Choice Index (836011004, Open Round)	**Experimental** RCT	Patients with psychotic disorders are often reluctant to start pharmacotherapy and once treatment has started up to 70% become non-adherent. Treatment recommendations are followed better, however, when patients are more involved in the decision-making process and are taken seriously. A good collaboration between patient and clinicians may improve adherence and thereby the long-term outcome of treatment. OBJECTIVES: To improve the involvement of patients in choosing their antipsychotic therapy. By making information available to patients concerning their medication they can weigh different pharmacotherapeutic options by means of a ranking list. The main objectives were: 1. the creation of a list of the top 10 selection criteria for tolerable antipsychotic medication, according to patients. 2. ranking of the available psychotic agents according to the individual selection criterion, and update the ranking list. 3. development of an online system that assesses patients' preferences, the Personal Antipsychotic Choice (PAC) Index. 4. Evaluation of the use of the PAC-Index. 5. Implementation of the PAC in practice.	**Completed:** Group sessions have been completed and the 15 most important adverse effects established. A top 12 of most used drugs was selected for which the 3 main effects were established using literature review. Antipsychotics were ranked on effect-size and frequency of side effects. Accuracy and usability were refined through testing with end users. A third version of the PAC-index was evaluated by patients, of whom 75% stated that they would use it. First analysis shows that patients using the PAC index are more satisfied than the patients in the traditional care group. The RCT for patient therapist communication is not yet completed. During the data collection period a complementary project was conducted, focused on subjective wellbeing when using different antipsychotics. Results for this are not yet available.

Title	Design (method)[17]	Description	Results
Optimizing pharmacotherapy by redefining the role of the pharmacist (836011025, Open Round)	**Experimental** Non-randomised controlled trial (pre/post comparison)	The prevalence of suboptimal prescribing of medications is considerable. Patients are often undertreated or subjected to interacting drug treatments that are potentially harmful. This frequently results in medication related hospital admissions that are potentially preventable. Improvements to the healthcare system are needed to maximise the benefits of pharmacotherapy. The integration of a pharmacist in the primary care, which has up to now not been studied in the Netherlands, could enable more efficient interventions to resolve drug therapy problems and help to build collaborative working relationships between pharmacists and physicians. OBJECTIVES: To study the effect and the feasibility of integrating a non-dispensing pharmacist into primary healthcare centres. In parallel to the prospective, non-randomized controlled intervention study, a qualitative implementation study was conducted. The aim of the implementation study was to systematically collect data on how the pharmacist practice model was implemented.	**Ongoing:** At the time of last reporting, the intervention period had not yet been completed so no results were available. Training programmes for pharmacists had been initiated.
Less may be more; reducing and rationalizing polypharmacy in schizophrenia (836021015, Open Round)	**Experimental** RCT	Though guidelines for the treatment of schizophrenia recommend antipsychotic monotherapy, 30% of patients are treated with two or even more antipsychotic drugs. The widespread use of antipsychotic polypharmacy may reflect some rationale of polypharmacy despite the lack of evidence to support this. For some patients, polypharmacy may be a better option than guideline recommended monotherapy. OBJECTIVES: To examine the effect of an algorithm based polypharmacy revision procedure in schizophrenia patients treated with at least 2 antipsychotics on all cause discontinuation of assigned treatment (primary outcome) and symptom severity, relapse rates, side-effects, functioning and health related costs (secondary outcome).	**Terminated:** This project was prematurely terminated because of insufficient inclusion of participants. There are multiple causes for this: 1) Practitioners were reluctant to include their patients for fear of relapse. 2) Participants that agreed to participate in the research found it unacceptable that they could be put in the control group. 3) Discrepancy between database and reality concerning polypharmacy in patients. 4) Budget cuts in health care led to a lack of availability and motivation of personnel.

Title	Design (method)[17]	Description	Results
"Why should I use my inhaler?" Development and testing of an adolescent adherence patient tool for asthma (ADAPT asthma - study). (836044002, Open Round)	**Experimental** RCT	Non-adherence to chronic medication is a complex problem due to the individual needs and wishes of patients. Little research has been done on adherence among young people, who are known to show poor adherence. Effective interventions to improve adherence are needed. OBJECTIVES: To create a smartphone application (for the patient) and a management system (controlled in the pharmacy) to promote therapy adherence. The app (ADAPT) will be created for adolescents that have asthma.	**Ongoing:** At time of last reporting, a first questionnaire had been completed by 235 youths, with no significant variation in the control and intervention groups on therapy adherence, asthma control, quality of life, perception of disease, or opinions on medication. 71% of participants in the control group, and 34% in the intervention group had completed the study and filled in the end questionnaire. Findings on impact on adherence are not yet available.
Tailored Pharmacotherapy			
Characterisation of the influence of (morbid) obesity on CYP3A-mediated clearance and oral absorption using midazolam as a model drug: towards evidence-based dosing in obesity (836011008, Open Round)	**Experimental** Non-randomised controlled trial	Midazolam is a drug that is widely used for sleeping disorders and with anaesthesia and sedation. However, to date, there are no data on the use of these kinds of (CYP3A) substrates such as midazolam on obese or morbidly obese patients. Heavier patients usually get higher doses but there is preliminary evidence that clearance of CYP3A substrates is lower in obese patients. This is a problem because it may result in prolonged effects of the drug with increased risk of the adverse effects. Moreover, obese patients are prone to sleep apnoea syndrome and respiratory depression. OBJECTIVES: To design and implement practical dosing guidelines for oral and intravenous midazolam in obese and morbidly obese patients, and for oral midazolam in patients that underwent gastric bypass surgery. The secondary goal was to study whether the derived dosing guidelines for midazolam can be extrapolated to other CYP3A substrates.	**Completed:** Clearance of midazolam in morbidly obese patients is no different than the clearance of non-obese individuals. The distribution volume increases strongly with increased body weight. Oral bioavailability of midazolam is doubled in patients with morbid obesity. Clearance increases in patients after gastric bypass surgery, while bioavailability stays the same. Metabolic capacity of the liver increases 15 times for CYP3A after gastric bypass surgery. Other CYP3A substrates will likely show the same trend. However, more research needs to be done on the internal blood flow of the liver of obese patients.

Title	Design (method)[17]	Description	Results
Treatment of patients with Fabry disease with agalsidase alfa and agalsidase beta: phenotypic diversity necessitates the development of individualized treatment guidelines (836011009, Open Round)	**Observational** Cohort study	There is a lack of high quality, long-term data on clinically relevant endpoints of the extremely expensive enzyme replacement therapy (ERT) for Fabry disease. This lack of data has hampered the identification of subgroups of patients that benefit the most from the therapy. This has resulted in an extremely unfavourable cost-effectiveness profile in the Netherlands, with questions rising about the reimbursement of the therapy. Discontinuation of reimbursement however, is not acceptable for patients who benefit from the treatment. OBJECTIVES: To optimize the appropriate use of costly intravenous ERT by individualising treatment in Fabry disease patients, thereby improving patient care. The collaborative research is expected to lead to the development of guidelines for the initiation, interruption and monitoring of specific patient groups. Moreover, the research will study the impact of antibody formation on clinical outcomes for two enzymes (agalsidase alfa and beta) and compare their effectiveness. Finally, the impact of vascular risk factors and co-medication, specifically the use of ACE/ARB inhibitors, on outcome.	**Completed:** Various factors were identified that affect enzyme therapy: kidney function, cardial mass and previous clinical complications. Results of the biochemical analysis were that therapy should begin in an early stage of the disease, is most effective in men with classical Fabry and that Agalsidase-beta is the preferred enzyme. Finally, results indicate that hypertension and high triglyceride may lead to clinical complications. Cardiovascular supporting treatments are very important.
Quality assessment of pharmacotherapy in patients with chronic kidney disease (836021013, Open Round)	**Observational** Cohort study, implementation pilot studies	Chronic kidney disease (CKD) carries a high burden for poor quality of life and high healthcare costs. Medication to reduce this burden is available but adequate monitoring of optimal use of such treatment is lacking. Quality indicators to evaluate medication treatment for CKD are needed. OBJECTIVES: To develop, validate and implement a comprehensive set of medication quality indicators for CKD patients. These indicators need to (1) assess medication treatment focusing on efficacy and safety aspects; (2) take into account differentiation for patient characteristics, such as age and disease severity; (3) be reliably measured using data collected from routine practice.	**Ongoing:** The 1st phase a list of 16 indicators was made. In the 2nd phase operational feasibility was tested in 4715 patients. Of the 16 indicators, 11 indicators had sufficient numbers of eligible patients for reliable calculation. Operational feasibility and validity of the indicators is being tested.

Title	Design (method)[17]	Description	Results
Goal oriented therapy with intravenous colistin to optimally treat infections with multidrug-resistant Gram-negative bacteria (COLIGO study) (836021008, Open Round)	**Observational** Prospective cohort study	There is a growing need for antimicrobial agents to treat infections with multidrug-resistant Gram-negative bacteria. Intravenous colistin has been re-introduced for this purpose, but evidence based guidelines to ensure effective and safe therapy are lacking. Recent data on the pharmacodynamics and pharmacokinetics of colistin give rise to a state of the art clinical pharmacological approach to individualize and monitor therapy. OBJECTIVES: To conduct a prospective observational study programme in relevant patient groups to enhance expertise with intravenous colistin in the Netherlands, to evaluate treatment efficacy and drug toxicity, and to develop and implement a treatment guideline.	**Completed:** There was a high inter- and intra-individual variability in the measured colistin plasma concentrations. In the cystic fibrosis group, controlled dosing led to a high level of effectiveness, while adverse effects were mild. For a significant part of the CF group a high daily dose is justified. The development of bacterial resistance was lower than expected. The results of the intensive care group could not be evaluated due to the small group of patients. Further study is therefore still ongoing.
Population PK/PD modelling to develop and implement guidelines to optimize safe and rational dosage of critical off-label drugs in critically ill premature infants (836011022, Open Round)	**Observational** Historically controlled study (in later stage, if guidelines are adapted)	Approximately 80% of drugs used in critically ill children in the NICU are used off-label. These drugs include compounds with potentially serious side effects and interactions. Recently, population PK/PD modelling and simulation studies enabled the development of evidence based, individualised dosing schemes for children, thus improving drug safety and efficacy OBJECTIVES: 1. To develop and implement dosing guidelines for 5 major off-label drugs in preterm infants <1500 grams and <32 weeks and bring together all expertise in this field in the Netherlands, 2. To develop an infrastructure for a paediatric PK/PD study Network in the Netherlands and develop a minimally invasive Dried Blood Spot analysis method to perform pharmacokinetic studies.	**Ongoing:** At the time of last reporting no (interim) analysis had been completed yet.
Identifying the right patient to treat, by estimating absolute treatment effect for individual patients based on randomised clinical trial data	**Other** Modelling	Instead of expressing the clinical significance of treatment in terms of relative risk at a group level, clinicians need to translate and apply evidence to an individual level. Patients vary greatly in characteristics that can affect the benefit they get from treatment. OBJECTIVES: To calculate individual patient level predictions of the change in absolute risk that can be achieved by treatment based on all relevant patient	**Completed:** Patients with intermediate vascular risk, vascular disease and type 2 diabetes have a large spread in the absolute treatment effect for prevention of cardiovascular diseases. Absolute treatment effect for patients with medium/high risk on

Title	Design (method)[17]	Description	Results
(836011027, Open Round)		characteristics. The goal is to identify patients at risk of cardiovascular disease who benefit most from medical treatment of blood pressure, lipids and antiplatelet therapy based on individual characteristics.	vascular diseases can be predicted using simple patient characteristics. With such prediction models patients that benefit the most of treatment can be identified. Cost effectiveness is higher for the treatment patients with vascular disease with lipid-lowering therapy.
Infrastructure			
The Pregnancy Drug Register: development and implementation (836012001, Registry)	**Other** Register development	More information on the safety of medical drugs used in pregnancy is needed to assess whether or not the benefits of drug use outweigh the risks. To increase knowledge, there is a need for monitoring of medical drug use during pregnancy. OBJECTIVES: To develop and implement a national register for prescription and over-the-counter medical drug use during pregnancy and pregnancy outcomes, such as miscarriage, stillbirth, birth defects, low birth weight and preterm delivery. This Pregnancy Drug Register will be used for: 1. Signal detection by systematically screening the register for combinations of drugs and pregnancy outcomes that are disproportionally present in the register compared to the rest of the database. 2. Conducting epidemiologic studies assessing associations between medical drug use and pregnancy outcomes.	**Completed:** A national pREGnant Pregnancy Registry for pregnant women and health care professionals has been constructed. Appropriate information materials such as invitations, flyers, brochures, letters and a website have been developed. The registry involves six dedicated questionnaires that can be completed over the internet. There are agreements with various parties in and around obstetric care to ensure that pREGnant is used in practice. Eight validation studies on the reliability of the collected information have been carried out.
Dutch south west Early Psoriatic Arthritis Registry (DEPAR-R) (836012002, Registry)	**Other** Register development	Psoriatic Arthritis (PsA) is a chronic, disabling inflammatory disease, associated with psoriasis, one the most common rheumatologic diseases. Approximately 30% of patients suffering from psoriasis will develop PsA on average 7 years after the onset of the skin disease. As a chronic disease with estimated lifetime risk of 0.5% for women and 0.6% for men, the disease is responsible for a fair share of the work load of rheumatologists and it has a significant financial burden on the health care system. OBJECTIVES: Development and implementation of an infrastructure needed for data	**Ongoing:** A central database has been created and is functioning according to the original description. At time of last reporting 364 patients had been enrolled. Patient 'trajectories' have been created to follow their progress. Data preparation for analysis on the initial study period had been completed and patient communication was set up.

Title	Design (method)[17]	Description	Results
		collection on psoriatic arthritis patients in order to describe the incidence and prevalence numbers of the disease in secondary care in the south-west of the Netherlands. The main outcome is disease activity, and secondary outcomes include cost-effectiveness of the applied treatment and drug survival. Furthermore, work participation and general well-being of the patients are subject of investigation.	
Implementation			
Transmural cooperation at hospital discharge to optimise continuity of patient care (836044008, STIP)	**Experimental** Non-randomised controlled study	The period after hospital discharge is a critical period for many patients. To address problems that arise during this period the guideline 'transfer of medication related information' has been published. However, the implementation of these guidelines has proven difficult. OBJECTIVES: To improve collaboration at the transition from hospital to home.	**Ongoing:** Pharmacist assistants have been given training on how to structurally explain medication changes. Community pharmacies have been given training for house visits. The new methods have started to be implemented in April 2016. The study has experienced some delays due to problems with inclusion.
Optimising adherence to the clinical guideline for diagnosis, pharmacological and psychological treatment of GGZ patients in long-term care as a breakthrough project (848022006, STIP)	**Experimental** Non-controlled experimental trial	Patients with serious psychological problems and a long history at GGZ are often on too much medication (e.g. polypharmacy, irrational combinations, interactions or toxic amounts). Due to this large amount of medication, patients are usually not able to lead a normal life. OBJECTIVES: To optimise guideline adherence regarding diagnostics, drug and psychological treatment for patients with serious psychiatric problems. By doing this, the irrational used of medication should decrease, improving the QoL of patients.	**Ongoing:** Preparatory activities, including development of the concept methodology are under way.
Implementation of therapeutic drug monitoring via dried blood spots in daily practice (836044004, STIP)	**Observational** Pilot study	At the moment, therapeutic drug monitoring and optimisation of an outpatient chronic treatment is a time-consuming process. However, the dried blood spot method (DBS) could potentially be more patient friendly and efficient as it can be done from the patient's home. OBJECTIVES: To speed up the implementation of DBS	**Ongoing:** Personnel has been trained and DBS information is improved. Pilot studies have started.

Title	Design (method)[17]	Description	Results
		for therapeutic drug monitoring of immunosuppressant's in transplant patients. Furthermore, training and information will be created for the patients.	

Appendix H Overview of awarded patient registry projects

Project title	Lead Organisation	Status
Dutch south west Early Psoriatic Arthritis Registry (DEPAR-R)	Albert Schweitzer Hospital	Ongoing
The Pregnancy Drug Register: development and implementation	Lareb	Completed
Pharmachild-NL registry	Twente University	Ongoing
Dutch Registry of Patients with Haemophilia and associated Disorders	LUMC	Ongoing
Epilepsy register	Epilepsy Centre Kempenhaeghe	Ongoing
A national registry for Systemic Lupus Erythematosus (SLE) in the Netherlands	VUMC	Completed
Development of a registry for improving rational use of pharmacotherapy for chronic hepatitis B and C patients	AMC	Completed
Adding in- and outpatient pharmacotherapeutic treatment information to a psychiatric case registry	Utrecht University	Ongoing
A patient register for botulinum toxin-A treatment in children with cerebral palsy	VUMC	Ongoing
IB-DREAM: Registry for inflammatory bowel diseases in The Netherlands	Radboudumc	Ongoing
Registry of Adult Patients with Severe asthma for Optimal DIsease management (RAPSODI)	AMC	Ongoing
Registry for spondyloarthritis in the Netherlands - SpA-Net	Maastricht UMC+	Ongoing
TREatment of ATopic eczema (TREAT) Registry Taskforce - Netherlands	AMC	Ongoing
Registration, evaluation and optimalisation, with feedback and follow-up of pharmacotherapy for all patients visiting a university hospital for evaluation of cardiovascular conditions: the Utrecht Cardiovascular Cohort	UMC Utrecht	Ongoing
Registry of cancer patients to monitor the impact of (pharmaco)therapy on health problems presented in primary care treatment on health problems presented in primary care	NIVEL	Ongoing
Early benefit risk evaluation of new medicines in primary care: Medication Benefit Risk Registry - overactive bladder (MedBRR-OAB)	NIVEL	Ongoing

Technopolis Group 2017, based on documents provided by ZonMw

Appendix I Assessment Procedure

The ZonMw assessment procedure follows eight steps, that are described below. Furthermore, each call has specific criteria proposals need to fulfil in order to be accepted. These are described in the GGG-programme text of 2015.

1. Call for proposals of project ideas to the field

   The call for proposals is communicated through the website, relevant journals, social media, e-mail and Mediator. A proposal for a project idea should be a maximum of 3 A4 pages, and should be written in English. Sometimes suggestions are provided for the drafting of a project idea.

2. Assessment of project ideas

   The different project ideas are assessed by the Rational Pharmacotherapy Programme committee. The assessment is for a large part based on relevance. The scientific quality will be roughly assessed. The result is either a positive or a negative advice to further elaborate the project idea into a subsidy request. It may happen that suggestions for further elaboration are given.

3. Subsidy request

   Based on the advice, a further elaborated subsidy request can be submitted through ProjectNet. The request should be written in English. The research question of the elaborated proposal may not divert from the original project idea.

4. Assessment by referees and response of submitters

   Every proposal, when fitting within the programme framework as described in the programme text, will be assessed by at least two independent experts. These referees provide a judgement on the relevance and quality. The submitters also receive the possibility to react on the assessment by the anonymised referees with a written response.

5. Judgement about the relevance and quality of the subsidy requests

   The programme committee determines a relevance-score and formulates a final judgement about the quality of the proposal, based on the anonymised assessments by the referees and the responses of the submitters. When determining the relevance, the judgement of the referees and the response by the submitter are weighted in.

   In the case of multiple proposals, the programme committee determines the priority of the different projects based on the assessment of relevance and quality, with relevance weighing heavier than quality. In order to be eligible for funding, a project should at least score 'relevant' and 'good quality'. This is displayed in a priority matrix (Table 14).

*Table 14 Prioritisation matrix**

Quality/ Relevance	Very relevant	Relevant	Low relevant
Very good	1	3	-
Good	2	4	-
Sufficient	-	-	-
Mediocre	-	-	-
Insufficient	-	-	-

Source: based on GGG-programme text (2015) (* = '-' means rejection)

In the ranking, based on relevance and quality, specific Rational Pharmacotherapy relevance criteria will also be taken into account. Finally, there is the possibility that the assessment considers the different priorities per subsidy-call. These call-specific priorities will be taken into account with each announcement of a new subsidy-call.

The ranking and the available budget are decisive for granting. With two or more high scoring proposals about a similar topic, it might be decided to only honour one in order to ensure enough diversification across topics. First, however, it will be attempted to realise a collaboration.

6. Adjustment of the project proposal

   With several proposals, that are in principle eligible for honouring, there is the possibility for a follow-up trajectory. This will entail the answering of subsequent questions or the adjustment of the project proposal. This will hold for projects that are assessed as mediocre, and – when there is sufficient budget – for projects that are eligible for honouring. A new assessment will follow with – where needed – (new) referees.

7. Remuneration/ rejection

   Based on the assessment and prioritisation the programme committee will propose a remuneration or rejection. Submitters receive formal commitment or a motivated rejection by the director of ZonMw, on behalf of the ZonMw board.

8. Start studies

   According to ZonMw procedures, studies should start six months after grant allocation.

Appendix J Methodology portfolio-analysis

Topic	**Process**
Data Source	The data stems from ZonMw. They have kept records and shared these with the evaluation team.
Data merging	We have merged the different datasheets to gain a holistic dataset of the entire GGG-programme (limited to those modalities for which data were collected). Some modalities were not categorised by thematic priority, others not by specialisation. Most of this has been corrected for retrospectively. In this process we have checked multiple times to ensure no errors were made in copying different fields.
Restructuring:	
Organisations	Organisations had different spellings or abbreviations of their name and were thus not standardised. We have, in consultation with the programme office, decided on set names for organisations which had multiple references and standardised this variable list.
Types of organisations	In order to know who collaborates with whom and who has the lead in projects, organisation types were added as a variable. This too was done in consultation with the programme office and became a reiterative process over the course of the evaluation, taking in feedback and suggestions from the modality committees and the Evaluation Commission. - Academia = UMC (academic hospital), university - Primary care = pharmacies, regional health services and primary care services - Centres of Expertise = information centres, interest organisations
Target groups	Target groups were indicated by the programme office. In cases where multiple target groups were indicated, our senior consultant re-evaluated on the basis of the project description and determined which target group was most relevant. In principle studies target the entire population, however, these subcategories have been added to identify where special focus was put on less-researched groups such as minorities and pregnant women. Projects in the modality Registries were always population wide unless explicitly indicated that they focussed on children or pregnant women.
Specialisations	Specialisations were attributed by the programme office. These too were changed somewhat over the course of the evaluation to accommodate feedback from the Evaluation Commission and the modality committees. Below are some further clarifications: - Cardiovascular = also inclusive of cardiology - Pediatrics = everything to do with children's health, including use of antibiotics - Neurology also inclusive of rehabilitation medicines
Rooms	The classification of thematic priorities was done retrospectively and has been limited to one thematic priority per project, even though some projects could be assigned to multiple categories. Although it is likely that some projects touch on several thematic priorities, allowing multiple categories would result in more funding being awarded to the different thematic priorities than there being available. All STIP projects were categorised as 'Implementation'. All Registries projects were categorised as 'Infrastructure'.

Appendix K Meetings organised or attended by representatives of the GGG-programme (in Dutch)

K.1 Meetings organised by the GGG-programme

Meeting	deelnemers	open/invit
2012		
Rediscovery meeting: presentatie rapportage	18	invitational
Startbijeenkomst GGG	100	invitational
Infobijeenkomst potentiële indieners	125	open
Infobijeenkomst potentiële indieners	94	open
Invitational off-label	20	invitational
Infobijeenkomst potentiële indieners	35	open
2013		
1e GGG-congres	280	open
HTA methodologie bijeenkomst	60	open
HTA thema bijeenkomst Value of Information	15	invitational
Expertmeeting patientenregistraties	70	open
Infobijeenkomst potentiële indieners	53	open
Bijeenkomst projectleiders PMO en PMK	50	invitational
2014		
Consultatie rondom patientenregistraties zeldzame aandoeningen	40	invitational
2e GGG-congres "Shared Value"	200	open
Infobijeenkomst potentiële indieners	17	open
Focusgroepen Innofarma goed gebruik specialistische geneesmiddelen	30	invitational
HTA thema bijeenkomst kwaliteit van leven	20	invitational
Bijeenkomst internationalisering HTA (organisatie ZonMw)	90	open
2015		
3e GGG-congres "Therapie op maat"	300	open
Infobijeenkomst potentiële indieners	99	open
2016		
Projectleidersbijeenkomst patiëntenregistraties	52	open
4e GGG-congres "Niet meer en niet minder"	400	open
Strengthening workshop grote trials	20	invitatonal
Infobijeenkomst potentiële indieners	30	open
2017		
Webinar potentiële indieners gezamenlijke ronde met Hartstichting	20	open
Bijeenkomst rondom overhandiging netwerk subsidie door Canadese ambassadeur	25	invitational
5e GGG-congres "Kennis van nu = inspiratie voor morgen"	500	open
Thyrax overhandiging rapport	20	invitatonal
Workshop datamanagement personalised medicine	20	invitational
Strengthening workshop grote trials	20	invitational
Infobijeenkomst potentiële indieners plus livestream	70	open

K.2 Meetings to which the GGG-programme contributed

Meeting	rol ZonMw	deelnemers	open/invit
2012			
Dutch Medicines Days (sessie met Nefarma en NVFG Real world data for the patient)	organisatie sessie(s)	-	open
2013			
DICA congres	presentatie	-	open
Annual Scientific Meeting of The Japanese Society of Clinical Pharmacology and Therapeutics	presentatie	-	open
Dutch Medicines Days (sessie met Nefarma&NVFG Exploring new models for stimulating pharmaceutical innovation, sessie over orphan drugs en sessie met NVKFB over drug rediscovery)	organisatie sessie(s)	-	open
Medical Advisors cursus (presentatie GGG registraties)	presentatie	15	open
2014			
Medical PHIT congres	presentatie	100	open
DICA congres	presentatie	-	open
Openingssymposium “Toename van geneesmiddel effectiviteit en veiligheid met vermindering van kosten?” ter gelegenheid van de oprichting van de nieuwe Afdeling Klinische Farmacie en Farmacologie UMCG	presentatie	-	open
Estland EuroBioForum 2014	presentatie	-	open
Dutch Medicines Days (sessie met Zilveren Kruis en Nefarma: Personalised Medicine, a giant leap for rational Pharmacotherapy	organisatie sessie(s)	150	open
ICORDrare disease international mtg (cocreation with GGG)	organisatie sessie(s)	-	open
Medical Advisors cursus (presentatie GGG registraties)	presentatie	20	open
2015			
Talkshow: proefpersonen gezocht Women Inc (deelnemer panel)	panel	60	open
Dutch Medicines Days (sessie met NVFG, Zilveren Kruis, AmCham: Van Protocollaire naar Gepersonaliseerde Therapie op Maat	organisatie sessie(s)	-	open
2016			
CIHR strengthening workshop reuma netwerk (in Canada)	presentatie	20	invitational
presentatie informatiebijeenkomst MUMC	presentatie	40	open
Dutch Medicines Days (presentatie James McCormack)	organisatie sessie(s)	-	open

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Bijlage 2: Samenstelling Externe Evaluatiecommissie

Leden van de commissie zijn op persoonlijke titel benoemd. De commissie bestaat uit deskundigen uit het veld, die op grond van hun wetenschappelijke of maatschappelijke positie oog hebben voor het betreffende aandachtsgebied. Zij functioneren als deskundigen zonder last of ruggenspraak. De benoeming is voor de duur van de opdracht waarvoor de commissie is ingesteld.

1. **prof. dr. H.G.M. (Bert) Leufkens,** voorzitter voorzitter College ter Beoordeling Geneesmiddelen (*tot 1 aug 2017*), hoogleraar Farmaceutische wetenschappen, Universiteit Utrecht
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