CBG MEB

MEDICINES EVALUATION BOARD

Programme MEB Regulatory Science Day 13 February 2020

Replacement, reduction and refinement of animal studies

Location: Jaarbeurs Auditorium, Utrecht

Programme

MEB Science day 2020
Replacement, reduction and refinement of animal studies

Chair of the day:
dr. Marjon Pasmooij, Science programme manager MEB

12.00 – 13.00	**Registration and lunch**
13.00 – 13.05	**Opening and welcome** drs. Hugo Hurts, executive director MEB
13.05 – 13.30	**Realising an optimal safety and efficacy assessment with a minimum of animal studies: MEB experience with 3Rs** dr. Peter van Meer, non-clinical assessor Pharmacology, Toxicology and Pharmacokinetics MEB
13.30 – 14.00	**Moving away from animal use: the IMI VAC2VAC project. Opportunities & challenges** dr. Coenraad Hendriksen, senior scientist Intravacc and emeritus professor Utrecht University
14.00 – 14.20	**Potency tests in animals are not precise. The inherent variability of in vivo potency tests for vaccines** Coen Stalpers, PhD student of Utrecht University and MEB, quality assessor MEB
14.20 – 14.50	**Break & Poster session**
14.50 – 15.20	**Applying the 3Rs in Toxicology and Regulatory Sciences** dr. Fiona Sewell, Programme Manager Toxicology and regulatory sciences, human health effects NC3R
15.20 – 15.50	**Advanced in vitro models for drug development: the complexity of simplicity** prof. dr. Roos Masereeuw, professor of Experimental Pharmacology Utrecht University
15.50 – 16.20	**Panel discussion** Facilitator: dr. Jan Willem van der Laan, senior assessor Pharmacology, Toxicology and Pharmacokinetics MEB
16.20 – 16.30	**Reflections on the day**
16.30 – 18.00	**Drinks & networking**

About

For many years the Medicines Evaluation Board of the Netherlands, together with a lot of other organisations, is involved in developments in Replacement, Reduction and Refinement (also known as '3R') in the use of animal studies in regulatory requirements for drug development. These developments aim to reduce the use of experimental animals, decrease the animals' suffering, improve the animals' welfare, and increase the use of alternative methods. Last year, a guideline from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has been changed, which will lead to a reduction of the number of animals that need to be used in drug development.

This MEB Science Day, we will discuss the different developments in 3R. We will ask ourselves and the audience: How can we leverage these developments in regulatory practice? What are the challenges and opportunities when it comes to animal reduction? What will the future bring?

During the day we will also present an overview of ongoing PhD projects with involvement of the MEB in close collaboration with academic partners and institutes.
You can find the abstracts of the posters that will be displayed in this program booklet.

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Location:
Jaarbeurs Auditorium (Media Plaza),
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Abstracts

Poster 1: Tradition reduces value for both animal and human in drug development

Authors

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Purpose

Failure in phase II and III clinical trials are mainly due to lack of efficacy, which can partly be attributed to non-predictive animal models. National and international laws and regulations exist to protect animals used for scientific purposes, e.g. Directive 2010/63/EU (European Parliament 2010). We evaluated how the choice of a specific animal model were reflected and assessed in Project application forms for animal procedures for scientific purposes in the Netherlands.

Methods

Thematic content analysis was used to assess animal model choice in Project applications issued in 2017-2019 by the national Central Authority to license holders Utrecht University, University Medical Center Utrecht, Radboud University and Radboud University Medical Center Nijmegen.

Results
In total 125 animal models were assessed. Common explanations to choose a specific model were that the model existed (79%); the availability of expertise (62%); similar disease pathology/symptoms (59%). The explanations were given across the non-technical summary, main text and appendixes of the project applications. Explanations for the implementation of the principles of replacement (prior *in vitro* studies), reduction (experimental design and statistics) and refinement (reduction of discomfort) were unspecific. Explanations why alternative approaches were thought insufficient arose from the need for a model that is comprised of complexity or intactness.

Conclusions
Current choice of a specific animal model seems based on tradition, rather than its potential predictive value for clinical outcome. A specific and standardized substantiation for the choice of an animal model will increase the value of both laboratory animal and human patient. This will lead to better science in drug development.

References
European parliament (2010). "Council directive 2010/63/eu on the protection of animals used for scientific purposes." Official journal l276 53: 33.

Poster 2: What drug effect to focus on?

Evaluation of the dose selection process for phase 3 trials for drugs intended for the treatment of diabetes mellitus type 2: a regulatory perspective

Authors
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Introduction

Recent cardiovascular outcome trials with anti-hyperglycaemic medicinal products suggest that additional cardiovascular benefit can be achieved independent of glycaemic control. Nonetheless, the dose of a new drug, intended for the treatment of diabetes mellitus type 2 (T2D), is typically based solely on the glycaemic on-target effects of a drug. It is currently unknown to what extent off-target effects are considered for dose selection. Therefore, we evaluated which drug effects are included in the dose selection process for drugs intended for the treatment of patients with T2D.

Methods

In the EU, all medicinal products intended for the treatment or prevention of T2D are registered centrally by the European Medicines Agency. For these medicinal products, we extracted all available information regarding the selection of the phase 3 dose range from European Public Assessment Reports (EPARs) and electronic drug application dossiers.

Results

A total of 14 medicinal products were included in the analysis, consisting of three drug classes; SGLT-2 inhibitors (n=4), dipeptidyl peptidase 4 (DPP4) inhibitors (n=4) and GLP-1 receptor antagonists (n=6). Predominantly the on-target parameters, HbA1c (n=14) and fasting plasma glucose (n=6), were used in the justification of the phase 3 dose range. For the off-target parameters bodyweight (n=4) was included most frequently in the dose justification. Multiple off-target effects were included in the dose finding studies (n=21) as efficacy variables: bodyweight (18), LDL-C (14), HDL-C (14), triglycerides (14), total cholesterol (13), waist circumference (11).

Discussion

As expected, justification of the phase 3 dose was mainly based on the glycaemic on-target effects HbA1c and FPG. Nonetheless, multiple off-target effects, such as lipid parameters, bodyweight- and blood pressure related efficacy variables are included in the dose-finding studies. Therefore, questions can be raised whether dose selection should be solely based on the on-target effects of a drug.

Poster 3: Impact of complex drug approval decision-making processes on safety-related regulatory actions for drugs approved by the European Medicines Agency

Authors

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Background

Decision-making processes for drug approval differ in their level of complexity depending on uncertainties about the underlying evidence experienced by regulators. We assessed whether complexity is associated with safety-related regulatory actions (SRRAs).

Objective

To assess associations between complexity of drug approval decision-making processes and safety-related regulatory actions.

Methods

Retrospective cohort study of 40 innovative drugs approved in 2009-10 excl. influenza vaccines. SRRAs: significant changes to market authorizations and product information until 31 Oct 2017, i.e. revocation, suspension, non-commercial withdrawal, non-renewal, Direct Healthcare Professional Communications, and restrictions of indications, contraindications and warnings. Complexity assessment was based on major concerns about clinical trial data, procedure duration, whether consensus was reached, and negative initial opinion. We fitted a time-to-event model for recurrent events based on likelihood, and estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) to compare levels of complexity adjusted for pre-approval exposure.

Results

We identified 14 DHPCs and 222 product information changes, of which 72 were considered significant. Complexity was low (n=11), medium (n=16), or high (n=13). When considering full follow-up, we did not identify an association: medium & high vs. low complexity aHR 1.2 (0.6-2.4). However, model fitting indicated a difference in risk of SRRAs up to vs. beyond 39 months of the drug life-cycle. Primary analysis showed that drugs with medium & high complexity of the drug approval process were initially (≤ 39 months) at higher and later (> 39 months) at similar risk of SRRAs. Secondary analyses for medium and high complexity separately showed an even lower risk for high vs. low complexity beyond 39 months.

Conclusions

The differential timing of regulatory actions between levels of complexity may indicate that regulators more actively monitor the risks of products with higher complexity.

Poster 4: Estimands: old wine in new barrels?

Authors

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Background

An estimand defines the estimation target for a trial through specification of the treatment, population, variable, population-level summary and strategies for intercurrent events. ICH E9 (R1) addendum suggests five strategies for intercurrent events.

Methods
We systematically evaluated what estimands, especially what strategies for intercurrent events, are advised in european medicines agency disease guidelines, used in sponsors' trials and additionally requested by the european medicines agency during assessment. We selected four therapeutic areas: nervous system, oncology, cardiovascular and respiratory diseases. For each we selected all guidelines with approved drugs, the most recently approved corresponding dossiers and regulatory questions.

Results
Strategies for intercurrent events were present in 18 (53%) of 34 guidelines, in all 34 sponsor documentations and in 15 (44%) of 34 sets of regulatory questions. Treatment policy was advised in 13 (38%) guidelines and applied in 9 corresponding sponsor documentations. Hypothetical was not advised in guidelines, but was the leading strategy applied in 25 (74%) sponsor documen-tations. Composite was advised in 3 (9%) guidelines and applied accompanied by another strategy in 2 corresponding sponsor documentations. Principal stratum was advised in 2 guidelines, but not applied in corresponding sponsor documentations While-on-treatment was not advised in guidelines, but was applied in 2 sponsor documentations. Of the regulatory questions, treatment policy was present in 2 (6%), hypothetical in 6 (18%), composite in 6 (18%), and while-on-treatment in 1 (3%).

Conclusion
Treatment policy was most often advised in guidelines, but hypothetical was the leading strategy applied in sponsor documentations. Thus, results indicate not a full concordance between the regulatory target of estimation and what is actually estimated.

Poster 5: A standardised framework to identify optimal animal models of disease in drug development

Authors

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Background

Poor translation of efficacy data derived from animal models can lead to clinical trials unlikely to benefit patients – or even put them at risk – and is a potential contributor to attrition in drug development.

Objectives

To develop a tool to assess, validate and compare animal models used for the preliminary assessment of efficacy.

Design and results

We identified eight key domains used in the literature to validate animal models: Epidemiology, Symptomatology and Natural History – SNH, Genetic, Biochemistry, Aetiology, Histology, Pharmacology and Endpoints. We designed the Framework to Identify Models of Disease (FIMD) to include standardised instructions, a weighting and scoring system to compare models as well as factors to help interpret model similarity and evidence uncertainty. We also added a reporting quality and risk of bias assessment in the Pharmacological Validation domain. We conducted a pilot study of the validation in two models for Type 2 Diabetes – the ZDF rat and db/db mouse. Finally, we present a full validation and comparison of two models for Duchenne Muscular Dystrophy (DMD): the mdx mouse and GRMD dog. We show significant differences between the mdx mouse and the GRMD dog, the latter mimicking the human epidemiological, SNH, and histological aspects to a greater extent than the mouse despite the overall lack of published data.

Conclusions

Fimd facilitates drug development by serving as the basis to select the most relevant model that can provide meaningful data and is more likely to generate translatable results to progress drug candidates to the clinic.

Poster 6: Adverse events related to biologicals used for patients with multiple sclerosis: a comparison between information originating from regulators and from the scientific community

Authors

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Background

Clinical decision making is facilitated by health care professionals' and patients' adequate knowledge of the adverse events. This is especially important for biologicals used for treating multiple sclerosis (MS). So far, little is known about whether different information sources report adverse events consistently.

Methods

We included biologicals authorised by the European Medicines Agency for the treatment of MS in this study. We compared information on adverse events, derived from the phase three clinical trials, from European public assessment reports (EPARs) and scientific publications.

Results

In the study, we included eight biologicals used for the treatment of MS for which the EPAR and/or scientific publication reported a total of 707 adverse events. Approximately one-third of the adverse events was reported in both the EPAR and scientific publication, one-third was only reported in the EPAR and one-third only in the scientific publication. Serious adverse events and adverse events that regulators classified as “important identified risk” were significantly more often reported in both sources as compared to adverse events not classified as such (respectively, 38% vs 30% and 49% vs 30%). Adverse events only reported in the EPAR or scientific publication were, in general, not described in the benefit-risk section or abstract, which we considered to be the most important sections of both documents.

Conclusions

This study showed that there is substantial discordance in the reporting of adverse events on the same phase three trials between EPARs and scientific publications. To support optimal clinical decision making, both documents should be considered.

Poster 7: Overall survival in advanced melanoma patients with brain metastases

Authors

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Advanced melanoma patients with active brain metastases have not been represented in phase iii clinical trials. They account for 68% of the patients treated in clinical practice but are considered non-eligible for immuno- and targeted therapy trials. Recently, post-approval clinical trials with targeted therapies have been performed in this specific subgroup. The aim of the current study was to compare the survival time of patients treated in clinical trials with patients treated in the real world.

From the registry database of the medicines evaluation board (MEB), clinical trials in advanced melanoma patients with brain metastases were selected. Treated patients in daily clinical practice were retrieved from the Dutch melanoma treatment registry (DMTR), a nationwide registry that includes all Dutch advanced melanoma patients. Patients with brain metastases diagnosed between 2013-2018 and treated with first line targeted therapy were selected from the DMTR. Clinical trial patients were then matched with real-world patients based on patient- and tumor characteristics using propensity score matching. Differences in median overall survival (mOS) were assessed by Kaplan-Meier analyses and cox-regression models for matched and unmatched patients.

We expected a difference in the mOS of unmatched patients treated in the real-world compared to those treated in clinical trials. Baseline characteristics of real-world patients could be worse, i.e. an ECOG of ≥ 2, than those of clinical trial patients. For matched patients we did not expect a difference in mOS, since these patients have the same characteristics.

Poster 8: Quantification of adverse drug reactions related to drug product switches in the Netherlands

Authors

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We performed a retrospective cohort study in the Dutch patient population to identify drugs with a relatively high number of these ADRs, correcting for the number of drug product switches. For this purpose, we analyzed drug product switches and reported ADRs related to switching between June 1, 2009 and December 31, 2016 for a selection of 20 drugs. We also compared pharmacovigilance analyses based on the absolute, switch-corrected and user-corrected numbers of ADRs. Data were obtained from the National Health Care Institute in the Netherlands and from Lareb, which is the Netherlands Pharmacovigilance Centre.

In total, 1,348 reported ADRs and over 23.8 million drug product switches were identified. There was no correlation between the quarterly number of ADRs and the number of switches. Furthermore, we found a mean number of 5.7 reported ADRs per 100,000 switches in the dataset. The number was relatively high for rivastigmine, levothyroxine, methylphenidate and salbutamol, with 74.9, 50.9, 47.6 and 26.1 ADRs per 100,000 switches, respectively. When comparing pharmacovigilance analyses using the absolute number and the switch-corrected number of ADRs, we demonstrate that different drugs would be identified as having a relatively high number of ADRs, and different time periods of increased numbers of ADRs would be observed. We also demonstrate similar results when using the drug user-corrected number of ADRs instead of the switch-corrected number of ADRs, allowing for a more feasible approach in pharmacovigilance practice.

Overall, this study demonstrates that pharmacovigilance analyses of switch-related ADRs leads to different results when the number of reported ADRs is corrected for the actual number of drug product switches. The number of drug users could be an acceptable alternative to the number of drug product switches to be used for such correction.

Poster 9: Towards computational modeling of estrogen receptor alpha-mediated signaling in carcinogenesis testing

Authors

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Estrogen receptor alpha (ERα) belongs to the nuclear hormone receptor family of ligand-inducible transcription factors, and regulates gene networks in biological processes such as cell growth and proliferation. Disruption of these networks, for instance with the non-genotoxic carcinogen 17β-estradiol (E2), can result in adverse outcomes such as unanticipated cell proliferation ultimately culminating in tumor formation. Since ER signaling is also involved in normal physiological responses, and not solely activated in adverse outcomes, it is essential to quantify relationships between different key events leading to a particular adverse outcome induced by non-physiological ER activation. To obtain this quantitative information on these key events, a technique is favored which can provide single cell information on all these events. For this purpose, we established fluorescent protein reporter cell lines with bacterial artificial chromosome (BAC) green fluorescent protein (GFP) transgenomics of important players in the ERα signaling pathway in context of cellular proliferation. In combination with advanced live cell imaging, these reporters can monitor the spatial and temporal dynamics of key events of ERα pathway activation, i.e. target activation and cell cycle progression, at a single cell level. This adverse outcome pathway-driven reporter platform allows us to quantify relationships between various different key events and the ultimate cellular adverse outcome, and to eventually integrate this dynamic signaling data in a computational model. In addition, these in vitro reporters can be used to screen e.g. drug candidates or other chemicals of concern for the potential of modulating ER activity and the likelihood of a non-genotoxic carcinogenic mode of action.

Poster 10: Registries to be used in the regulatory decision-making process, what is minimally needed?

Authors

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Introduction

In the field of regulatory decision-making registries can be used to collect more data about the efficacy and safety of medicinal products.

Methods

We submitted a survey to pharmaceutical companies, regulators with experience in registries, registry owners, patients and Health Technology Assessment bodies to investigate what should be the minimal set of key parameters that are needed to answer most common uncertainties remaining at approval. Questions were asked about common data elements, data quality, governance and registry-based studies.

Results

Seventy-three participants completed the survey. Most of the responders work in the pharmaceutical industry. The most important demographic data to collect are gender, death, age and current pregnancy. For the medication important details to record are the dosage, the substance and the reason to start or stop the medication. Participants would not collect all adverse events. The collection of serious adverse events advents or adverse events of special interest are considered more important. The preference is to measure endpoints twice a year. All participants are willing to share the data with regulatory authorities. However, participants not working in the pharmaceutical industry are less willing to share the data with pharmaceutical companies.

Conclusion

In general the stakeholders do have consensus about the information that can be collected in a registry. For the collection of the use of medication and the reporting of adverse events guidance might be needed for the usefulness of the data for regulatory purposes.

Poster 11: A systematic review on intrauterine exposure to biologics in inflammatory autoimmune diseases

Authors

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Background

Inflammatory autoimmune diseases are chronic diseases that often affect women of childbearing age. Therefore, detailed knowledge of the safety profile of medications used for management of inflammatory autoimmune diseases during pregnancy is important. Nevertheless, in many cases the potential harmful effects of medications (specially biologics) during pregnancy (and lactation) on mother and child are not fully identified.

Objective

Our aim was to update the data on the occurrence of miscarriages and (major) congenital malformations of biologics based on newly published articles (from 01-01-2015 till 04-07-2019).

Material and methods
A search was conducted at 18-10-2017, 21-11-2018 and then 04-07-2019 in Embase.com, Medline Ovid, Web of science, Cochrane CENTRAL, and Google scholar with specific search terms for each database. Selection of publications was based on title/abstract and followed by full text (double blinded, two researchers). An overview was made based on outcomes of interest. References of the included publications were reviewed to include and minimize the missing publications.

Results and conclusion
A total of 143 publications were included. The total number of cases ranged from 9 for Canakinumab to 4276 for Infliximab. The reported outcomes were mainly miscarriages and (major) congenital malformations.

Despite limitations of our study, such as heterogeneity because of prospective or retrospective data and quality of the included publications, no major safety issues were reported and no trend could be observed in the reported malformations. Rates of major congenital malformations for investigated biologics were not higher than this rate in the general population.

Poster 12: Breakthrough therapy designated oncology drugs: are they rightfully criticized?

Authors

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Background

Regulatory agencies provide access to programs that facilitate earlier availability of promising drugs. One of these programs, the breakthrough therapy designation (BTD) of the Food and Drug Administration (FDA), has recently been criticized. The aim of this study was to determined whether breakthrough therapy designated oncology drugs were truly a breakthrough, based on the outcome of a validated instrument to measure clinical benefit.

Methods

New drug approvals for breakthrough therapy designated oncology drugs were identified via Breakthrough Therapy Approvals reports. Drug Approval Packages were used to obtain information regarding the pivotal clinical trial(s) supporting approval and the use of expedited programs. European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS) scores were assigned to clinical trials investigating breakthrough therapy designated drugs.

Results

A total of 18 breakthrough therapy designated drugs indicated for the treatment of patients with a solid tumor were identified in the Breakthrough Therapy Approvals reports. Approvals were supported by data from either phase I (n=2), phase II (n=12) or phase III trials (n=4). Of the 18 clinical trials investigating breakthrough therapy designated oncology drugs, 5 were assigned a high ESMO-MCBS score (ESMO-MCBS score: 4).

Conclusion

A few drugs were likely a breakthrough, based on ESMO-MCBS scores. This suggests that there is room for improvement. Nevertheless, determining clinical benefit is not always straightforward, given lack of confirmatory studies and use of surrogate endpoints. Despite not all drugs showed substantial improvement over existing therapies, several are incorporated in guidelines, reinforcing their relevance in clinical practice.

Poster 13: An insight in the inherent variability of in vivo potency assays for the DTaP vaccine

Authors

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Purpose

In vivo potency testing has remained the golden standard since the development of DTaP vaccines. The animal-based tests have shown their value ensuring safety and potency of several life-saving vaccines. However, they do have some shortcomings. Although in principle each assay is subject to variability, the variability of *in vivo* assays is generally considered to be high, however, there is little quantitative data available on the actual variability of *in vivo* assays. In the current study, we focus on the quantification of the variability of the *in vivo* assays used for the potency testing of DTaP vaccines.

Methods

Historical *in vivo* potency test results for DTaP vaccine were obtained from the registration dossiers available at the CBG-MEB (common technical documents, module 3, Method validation and stability data). One way ANOVA was used to establish the variance of the data sets. For the various antigens different assay types are used. The %CV (Coefficient of Variation) was calculated to allow comparing variability of different types of assays . In addition to variability between repeated tests on single batches also variability between potency results of different batches was analysed.

Results

Data for a total of 25 assays combined from four DTaP products has been analyzed. The determined %CV for within batch variability were ranging from 16.4% up to 131.7%. Only three assays score a %CV ≤ 20%. Furthermore, when the average potency results of the different vaccine batches are calculated, there is no significant difference between batches from the same process.

Conclusion & discussion

With our analysis we have quantified the high variability of *in vivo* potency tests for the DTaP vaccine. This shows the limitations of *in vivo* potency tests for quantitative monitoring of potency. It also provides a yardstick for variability for alternative methods that are developed to replace *in vivo* methods.

The absence of significant differences between batches of the same product shows that the production process of each of the four multivalent vaccines is consistent and well-controlled. This is supportive for the consistency approach that proposes to omit *in vivo* testing and monitor process consistency in combination with other release tests instead.

Poster 14: What does cell therapy manufacturing cost?

A framework and methodology to facilitate academic and small-scale cell therapy costings

Authors

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Recent advances with cell-based therapies (CBTs) hold great promise in the treatment of patients with rare and high burden disease. Currently the majority of CBTs are developed and manufactured in specialized and academic facilities. The continued expansion of CBT applications will progressively stress health care budgets. As a result, biomedical researchers and clinicians are increasingly faced with cost considerations in CBT development.

The objective of this research is to develop a costing framework and methodology for academic and small-scale cell-based therapy manufacturing facilities.

We conducted an international multi-center costing study in four different facilities in Europe using eight different CBTs as case-studies. This study covers the costs from procurement of cell material until release of end product. First, via interviews with clinicians, biomedical researchers, pharmacists and technicians (hereafter developers) we designed a framework. Next, we developed a more detailed uniform methodology to allocate cost items.

Cost were divided in facility running cost and operational cost and thereafter in cost categories: materials, equipment, personnel and facility. The methodology was tested via the case studies and validated in interviews. Costs are expressed in 2018 Euro's (€).

The framework and methodology was applicable across facilities and proved sensitive to differences in product and facility characteristics. Case study cost estimates ranged between € 8,673 and € 54,451 euro's per treatment. The cost estimations revealed hidden cost to the developers and provided insights to design best-practices. This framework and methodology can be used to inform and plan cost-conscious strategies.

Poster 15: Demographic and clinical factors that impact importance attached to drug effects: a preference study among type 2 diabetic patients

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Background
About 50% of patients with type 2 diabetes (T2D) do not reach their glucose (HbA1c) treatment targets. Differences in patient preferences may be a reason for such low target achievements. Preferences may be influenced by demographic and clinical factors.We aim to evaluate to what extent such factors influence the importance patients attach to certain drug effects.

Methods
A cross-sectional survey was administered to adult T2D patients in The Netherlands and Turkey. The anti-diabetic agents were described by six attributes: HbA1c decrease, cardiovascular risk (CVR) reduction, weight change, gastrointestinal (GI) adverse drug events (ADEs), hypoglycaemic events and bladder cancer risk (BCR). Multinomial logit models with treatment attributes and patient characteristic interactions were fitted for each of the factors.

Results

The survey was responded by 381 patients, 52% were Dutch. Median age was 63, 45% were male, mean BMI was 29 and 35% were higher educated. Median diabetes duration was 9 years and 19% reported experience with ADEs. Drug preferences varied strongly between country and age. Turkish patients valued more reducing CV risk while Dutch patients preferred to not having GI ADEs and reducing hypoglycaemic events. Younger patients valued more reducing CVR and no increasing BCR, while older patients preferred to maintain body weight and not having GI ADEs. Experience with ADEs, sex, BMI, and diabetes duration were marginally associated with drug preferences. Education did not show any effect.

Conclusions

The observed heterogeneity should be acknowledged when prescribing drugs in order to increase treatment satisfaction, adherence and therefore treatment outcome.

Poster 16: Drug safety issues covered by lay media, a cohort study of Direct Healthcare Provider Communications sent between 2001 and 2015 in the Netherlands

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Introduction

Some drug safety issues communicated through Direct Healthcare Professional Communications (DHPCs) receive substantial media coverage, while others do not.

Objectives
To assess the extent of coverage of drug safety issues that have been communicated through DHPCs in newspapers and social media. A secondary aim is to identify determinants that are associated with media coverage.

Methods
Newspaper articles covering drug safety issues communicated through 387 DHPCs issued from 2001 till 2015 were retrieved from Lexis Nexis Academic™. Social media postings were retrieved from Coosto™ for drugs included in 220 DHPCs issued from 2010 till 2015. Coverage of DHPCs by newspapers and social media was assessed in the two months respectively 14 days after issuing the DHPC. Multivariate logistic regression was used to assess potential DHPC- and drug-related determinants of media coverage.

Results
We found that 41 (10.6%) DHPC-safety issues were covered in newspaper articles. Newspaper coverage was associated with drugs without a specialist indication (ORadj 5.32; 95% CI [2.64-10.73]) and had received market approval drug age (3-5 years 0.30; [0.11-0.82], 6-11 years 0.18; [0.06-0.58]), and year of the DHPC (0.88; [0.81-0.96]). In the social media 180 (81.8%) drugs mentioned in 220 DHPCs were covered. Social media coverage was associated with drugs without a specialist indication (6.92; [1.56-30.64]), and for DHPCs communicating clinical safety issues (5.46; [2.03-14.66]).

Conclusions
Newspapers covered a small proportion of DHPC-safety issues only, but social media coverage was much larger. Coverage was associated in both media types with drugs that did not require a specialist prescriber.

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