



Involvement in Recent Developments

Statistics Leaders Meeting
June 11, 2014
Basel

Topics

Topic
<ul style="list-style-type: none">• Recent Data & Design Developments:<ul style="list-style-type: none">○ IMI: <u>GetReal</u>, IMI2○ EFPIA: New Clinical Trial Design Task Force○ EMAs Parallel Scientific Advice Regulators + HTA○ EMA PAES Working Groups○ Big Data – Real World Data

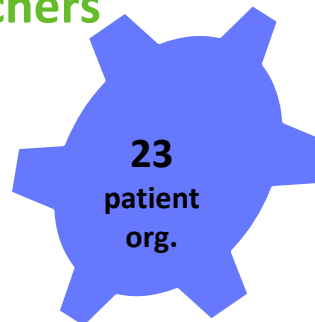


IMI2 - Establishing Europe as a world leader in medicines development

- Target identification and biomarker research (efficacy and safety)
- Driving the adoption of innovative clinical trial design
- Innovative Medicines
- Patient tailored adherence programmes

The IMI Community

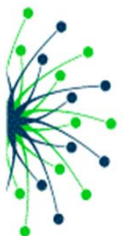
over 6000 researchers



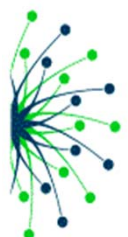
61% of projects
reported some form of
**PATIENT
INVOLVEMENT**

REGULATORS ON BOARD OF
12
PROJECTS

50% of projects have
REGULATORY AUTHORITIES
representatives in Scientific
Advisory Boards



IMI's ongoing projects



www.imi.europa.eu/content/ongoing-projects



The IMI Portfolio

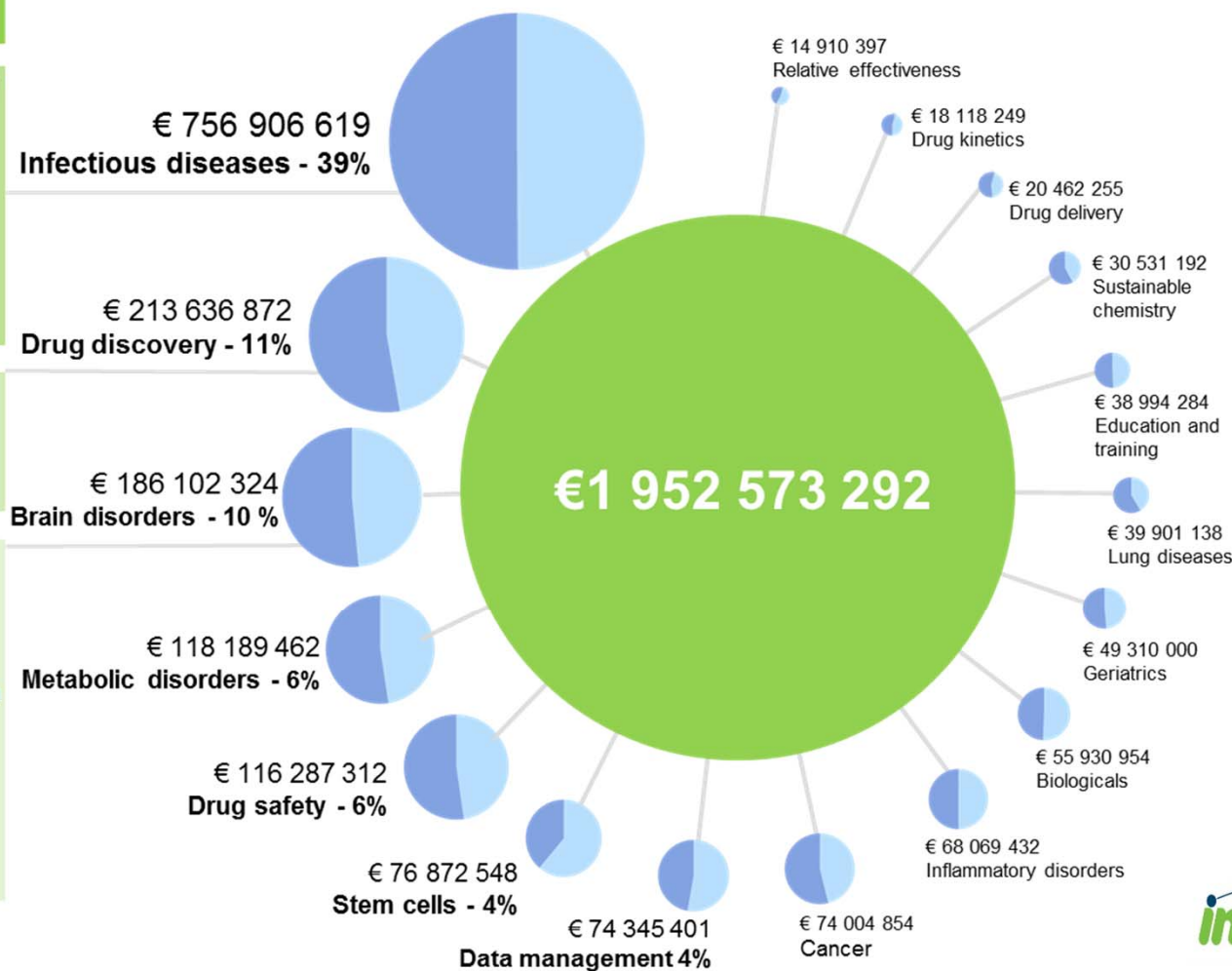
■ Corporate contribution ■ IMI funding

Partners

AiCuris	Johnson&Johnson
Animal Health	Medimmune
Division of Sanofi	Merck
Astellas	Merck Sharp & Dohme Corp
AstraZeneca	Merial
Basilea	Novartis
BoehringerIngelheim	Pfizer
Cubist	Rempex
GSK	Sanofi
Janssen	

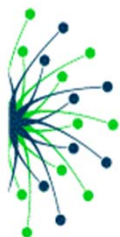
AstraZeneca	Novartis
Bayer	Pfizer
Janssen	Sanofi
Lundbeck	UCB
Merck	

Abbott	Janssen
AbbVie	Lundbeck
AC IMMUNE	Merck
Amgen	Novartis
Astellas	NOVO NORDISK
AstraZeneca	Orion Corporation
BIOGEN IDEC	Pfizer
BoehringerIngelheim	Roche
Eisai	Sanofi
Eli Lilly	SERVIER
ESTEVE	UCB
Grunenthal	Vifor
GSK	



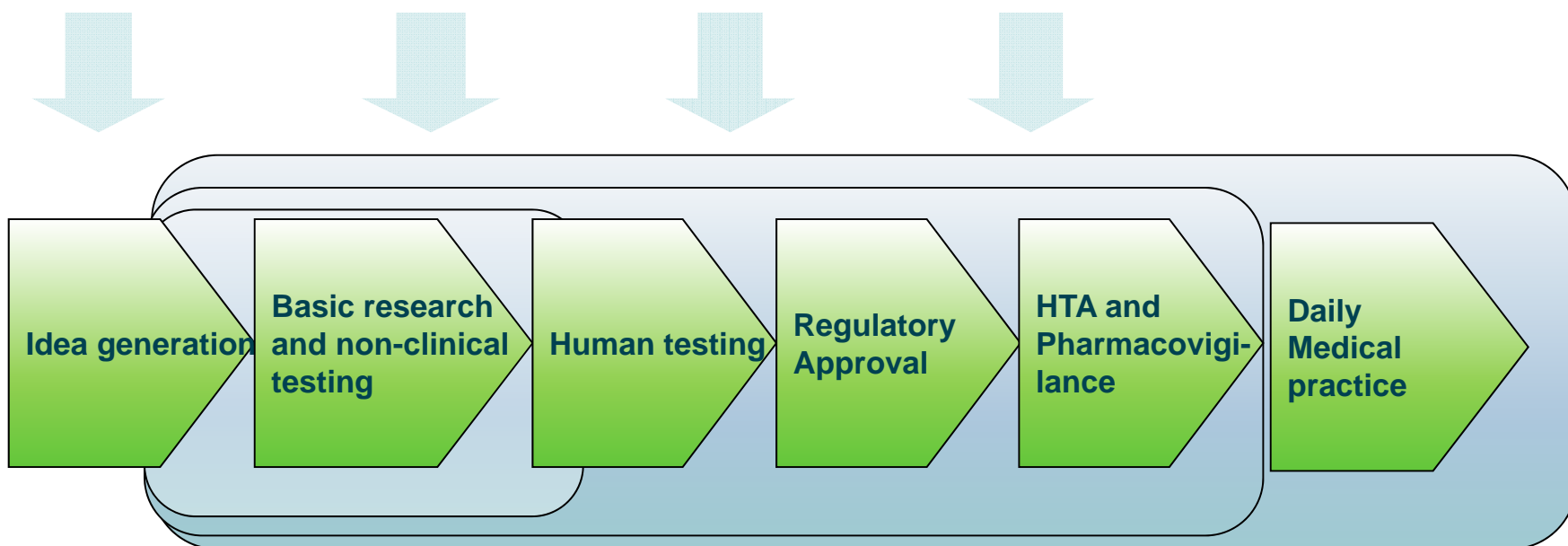
Clinical trials- improved design & process

Schizophrenia Depression	NEWMEDS	proposed reduction in duration of schizophrenia trials from 6 to 4 weeks
		proposed reduction in number of patients required in schizophrenia trials from 79 to 46
		developing new approach of combining medication with therapy
Alzheimer's Disease	PHARMACOG	new clinical study designs proposed and under investigation
Chronic Pain	EUROPAIN	optimizing clinical trial design to reduce placebo response
Rheumatoid arthritis	BT-CURE	Provided recommendation for terminology to be used to define specific subgroups of RA patients during different phases of disease
Autism	EU-AIMS	creation of pan-European clinical investigator networks
Asthma	U-BIOPRED	involving patients in clinical trial design
		established network of excellence in bronchoscopy in severe asthma
		generated central registry of patients with severe asthma
KM	EHR4CR	issued guidelines for writing the eligibility criteria
		developing the protocol feasibility service/demonstrator
		identification and assessment of eligible patients through EHR
Antibiotics	AMR program	creation of pan-European clinical investigator networks
		aims to develop new clinical study designs



The Evolution of IMI: From bottlenecks in industry – to bottlenecks in Industry and Society

Make Drug R&D processes in Europe more efficient and effective and enhance Europe's competitiveness in the Pharma sector

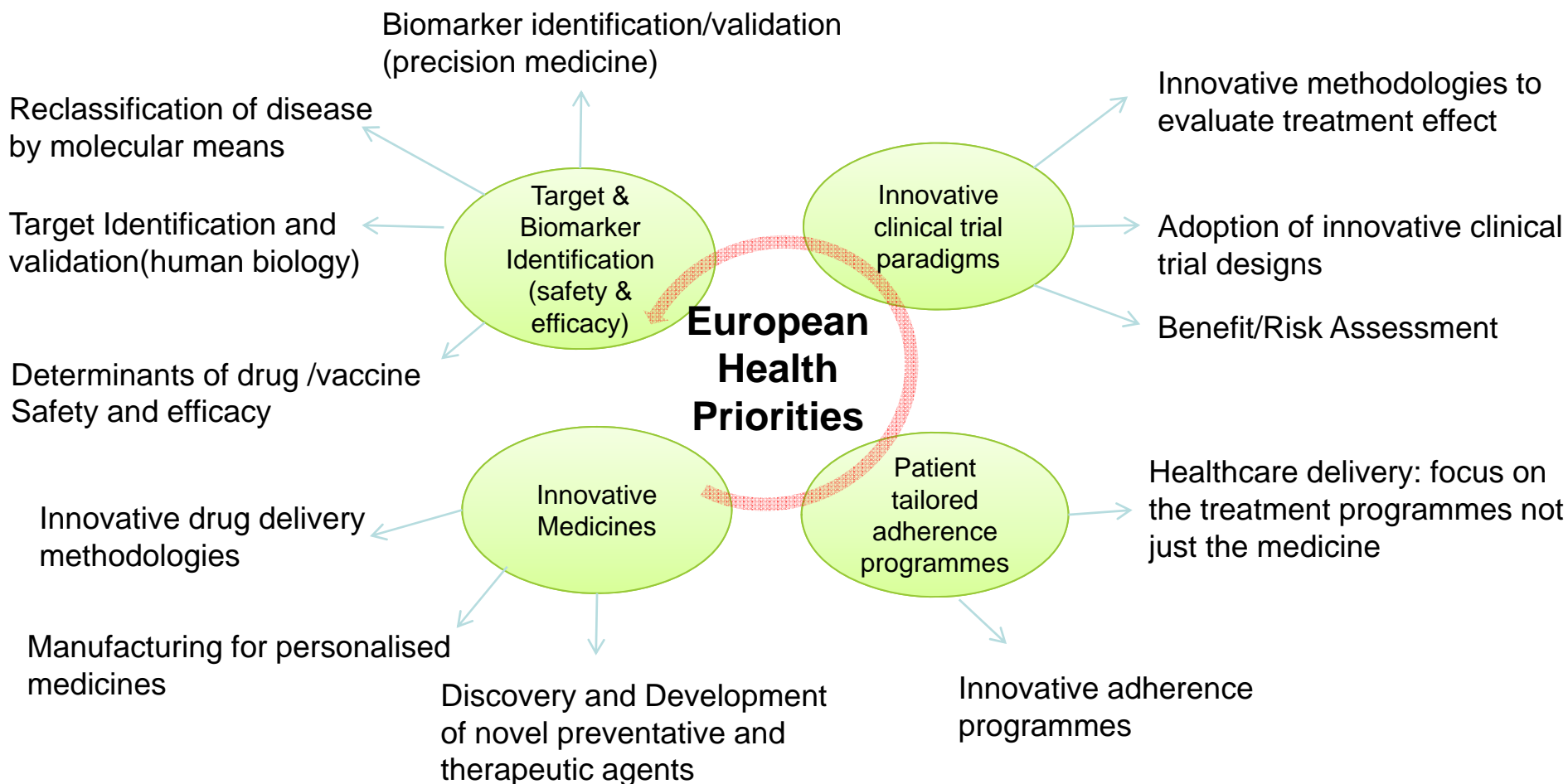


Primary focus of early IMI calls
2007 SRA

Shift to also addressing challenges in society and healthcare
2011 SRA

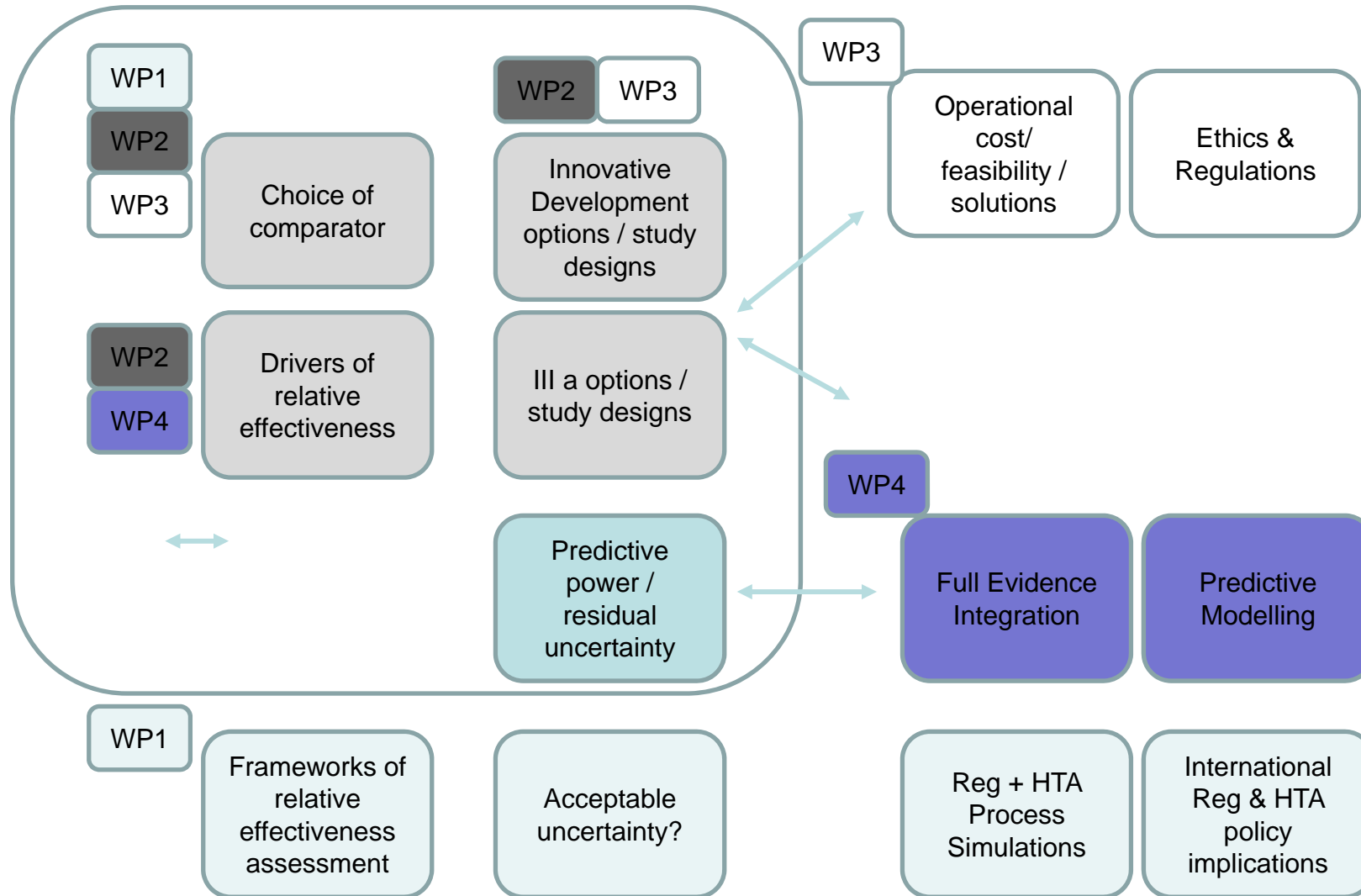
IMI 2 includes real life medical practice
2013 SRA

Major Axis of Research

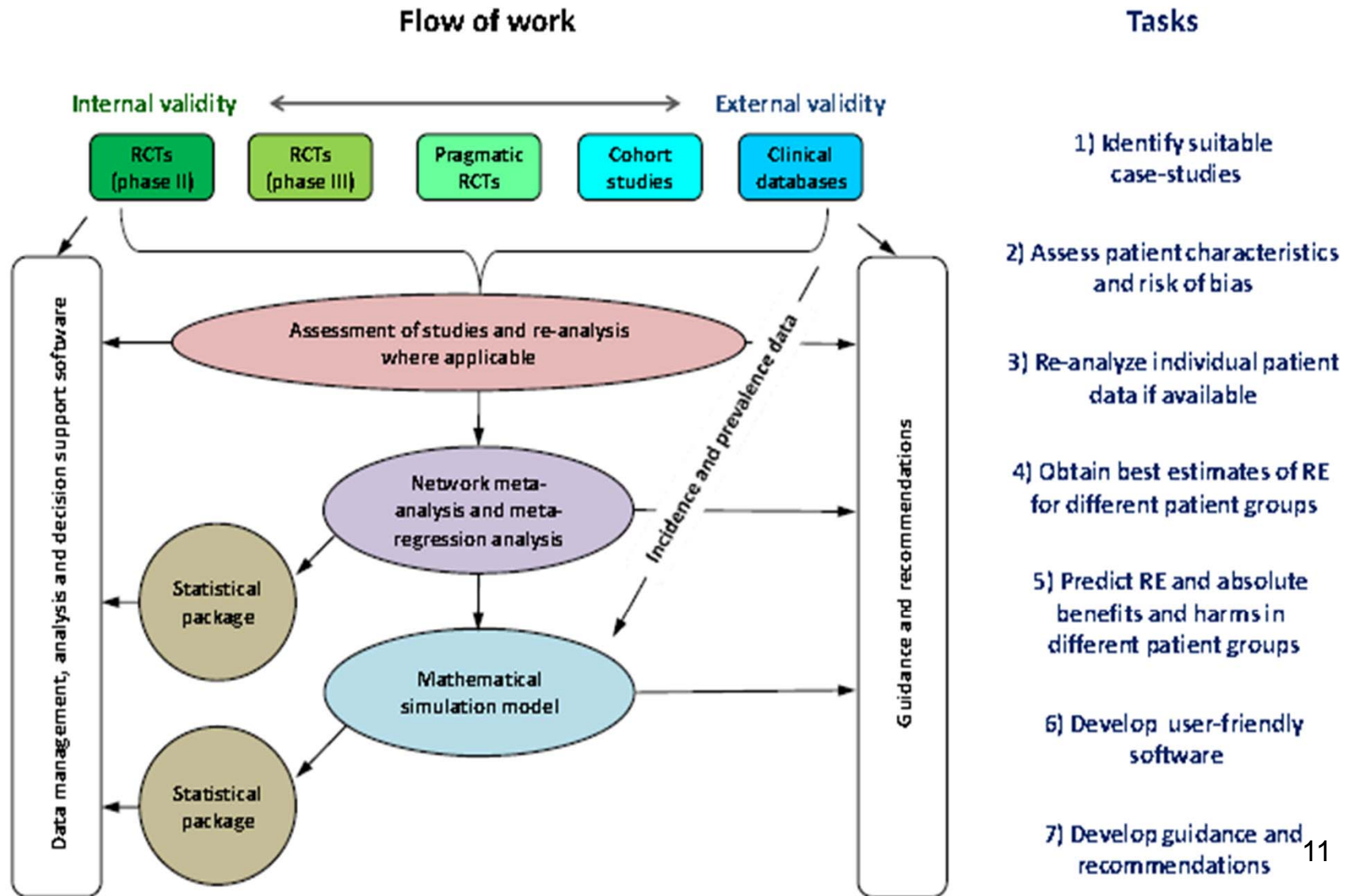


Drive change in delivery of medical practice

Structure and topics of GetReal

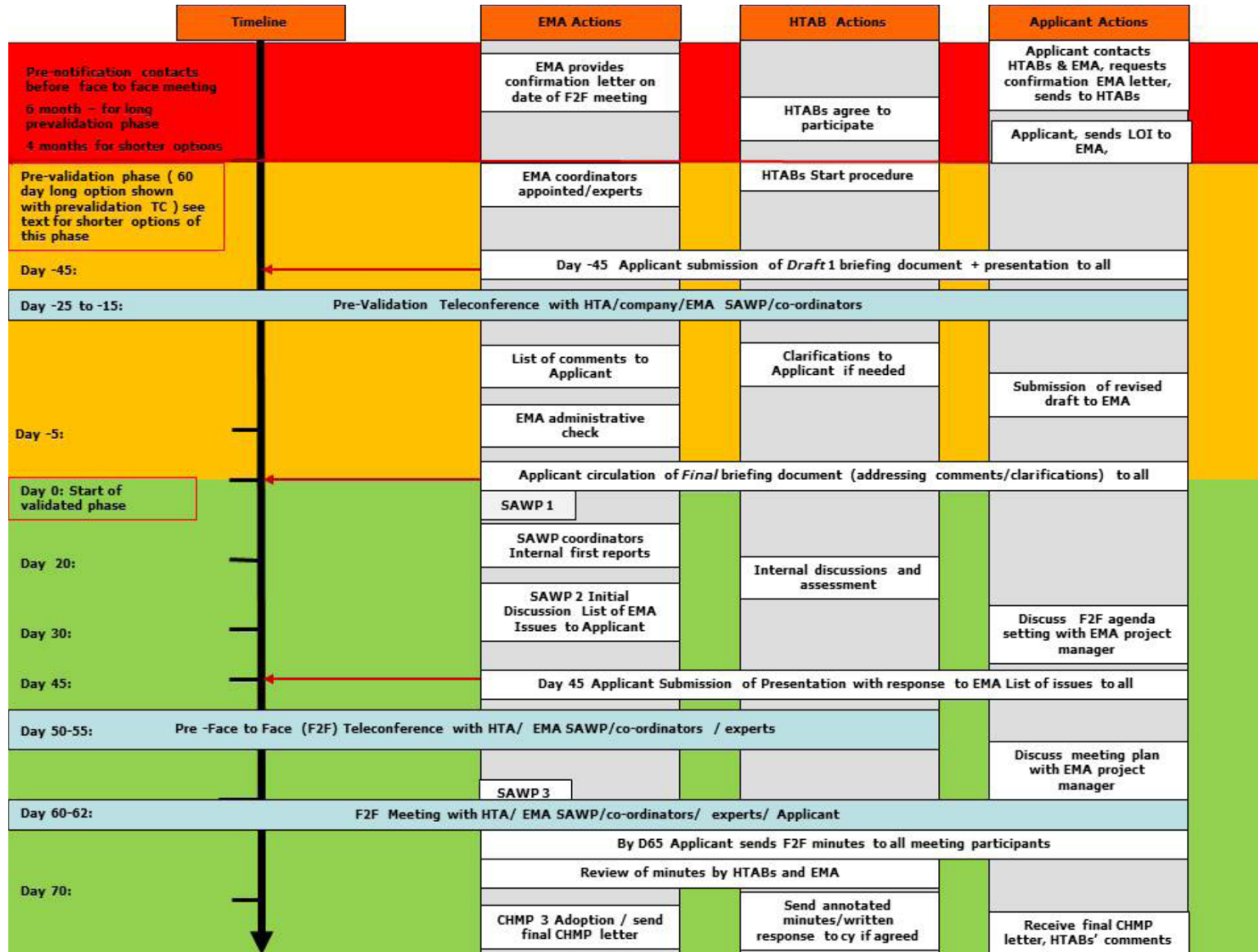


Developing a predictive model for relative effectiveness



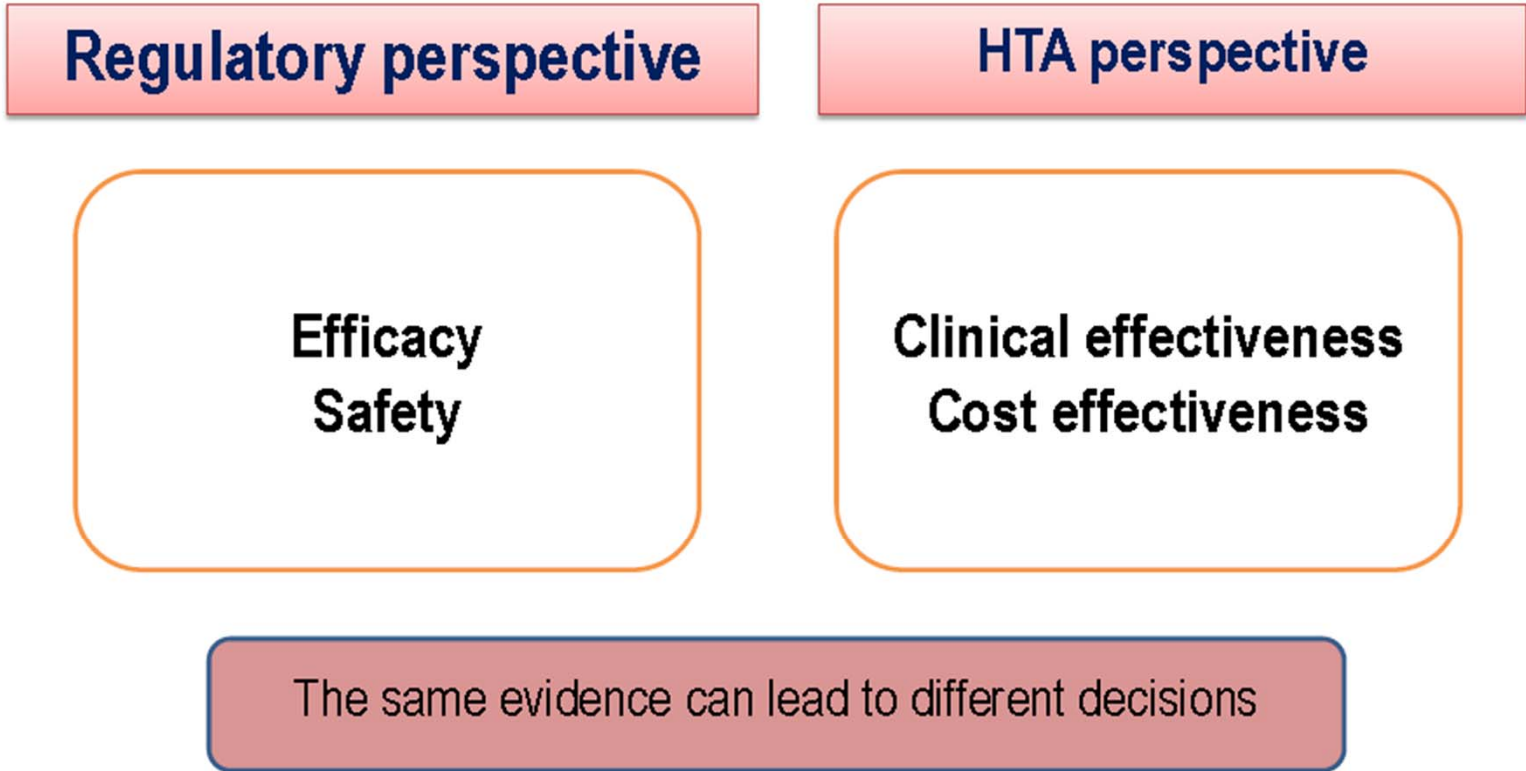


EMA-HTA parallel scientific advice



The HTA View

The HTA/Regulatory divide?



The HTA/Regulatory divide?

Regulatory perspective

HTA perspective

Not a divide but a continuum
of evidence development

Ef **ctiveness**

Safety **Cost effectiveness**

Parallel advice on evidence development at an early stage should reduce the likelihood of different decisions and provide a better pathway from laboratory to market for new medicines as well as the provision of 'value for money' in healthcare delivery

Regulatory View

For discussion - where to look for efficiency gains?

- Exploratory development. Too early?
- Promote that post-authorisation studies that meet everyone's needs. Too late?
- Start to build information for HTA into confirmatory trials?
 - More external validity to Phase III trials?
 - Additional assessments?
- Must not confuse roles and responsibilities, increasing hurdles, just because of a common development track

For discussion - the single development track

- Which HTA need? Regulatory system more practiced in harmonising between EU member states.
- Longer studies, multiple active comparators, clinical outcome variables, broader populations etc.
 - Increase variability and decrease sensitivity to drug effects; neither necessary nor proportionate for the regulatory question
 - No compromise on bias or error control
 - Adaptation of studies after the 'regulatory' question is answered
- Harmonise certain standards in advance – therapy area guidelines

For discussion - the single development track

- The role of the active control – why does one suffice?
- Assessment burden for the trial participants; opportunities in targeted data collection and monitoring
- The single analysis track
 - Format for data collection and storage
 - Key data for targeted trial monitoring
 - Analysis plans
 - Data presentations and summaries
- On the justification that ‘we need it for HTA’ and on compromise to agree a feasible development programme

Key Considerations of EMA-HTA Parallel Advice

Benefits

- * One Collaborative discussion
- * Input on which HTAs attend
- * Commonality of issues discussed;
 - * Comparators, end-points, PROs, Follow-up etc
- * Simultaneous feedback
- * Value in Regulators and HTAs hearing from each other
- * Understanding of similarities & differences of stakeholder requirements

Areas for Improvements

- * Sustainable process with clear owner
- * More consistent & predictable HTA engagement
 - * Attendance & Experience
- * Appropriate time to allow discussion of issues arising
 - * Identify alignment and discussion on differences
- * Clear output from HTA advice needed: similar to CHMP SA letter

SEED: Shaping European Early Dialogues

- HAS (lead) + 13 partners
- Regulators, payers, patient representatives as observers.
- Sustainable process to put in place, including collaboration with EMA
- Kick-off meeting (D1): October 21, 2013
- Preliminary work : procedures and templates for Briefing Books (medicines, MDs)
- All EDs in 2014, interim report after 5 EDs

Scenarios to test

- Independent advice and
- Parallel EMA-HTA advice

Model for permanent ED activity to be proposed



Post-Authorisation Efficacy Studies (PAES)

Methods for efficacy studies in the everyday practice

- Pragmatic trials
- Observational studies
- Registries
- Use of electronic health records in pragmatic trials
- Methods to control for confounding

1. Pragmatic Trials

- Pragmatic trials are randomised trials where patient follow-up is akin to an observational study.
- External validity and generalizability important
- Less appropriate where efficacy is uncertain
- Impact of the Clinical Trials Directive on the feasibility of pragmatic trials in practice
- Reliability of initial diagnosis by a GP

1. Pragmatic Trials - conclusions

- More use of Baskerville type designs where patients determine how long they stay in any arm of the trial before switching or withdrawing
- Use of 'Latin-square' designs and use of remote electronic follow-up for events of interest
- Cluster randomised trials for studying rare events
- Stepped-wedge designs introducing a drug in one area first and then randomising it sequentially in other areas
- Adherence to the CONSORT crucial for reporting results



2. Observational Studies

- Useful to study effect modifiers, namely variables that may influence the level of efficacy of the drug
- Useful when a rapid answer to an efficacy question needed using historical data or standard of care/reference changes over time
- Designing studies to increase the confidence in the reliability of results
- Require exposures and outcomes with a high specificity which can be measured with objective criteria



2. Observational Studies - conclusions

- Use same outcomes as those used to prove efficacy in RCTs
- Correctly measure the relevant confounding factors and effect modifiers
- Intention-to-treat analysis should always be performed but other analyses may be important
- Credibility of results could be increased with documented use of strict standards of quality control

3. Registries

- Registries allow collecting data on patients diagnosed with a certain disease or treated with a certain drug in a defined setting
- Important for understanding real-world and off-label use
- Allow for wide variety of study designs
- Allow for large numbers of subjects to be followed, e.g. rare safety events, treatment heterogeneity
- Various limitations so their use needs careful consideration



3. Registries - conclusions

- Data quality is key for success
- Common terminologies and data dictionaries/definitions, quality control of laboratory and measuring data and standards for collection of patient-reported information increase the validity of the results
- Describing the representativeness and generalizability of a registry is key for interpretation and reporting



4. Use of EHR for pragmatic trials

- Using clinical practice databases to facilitate the conduct of randomised clinical trials is a new area and that significant challenges need to be resolved
- Most benefit where outcome can be accurately recorded allowing low-cost long-term follow-up
- Limitations include existing EHR systems vary in terms of structure, set-up, accuracy and QC



4. Use of EHR for pragmatic trials - conclusions

- Harmonisation of legal requirements and administrative procedures across databases
- Development of software to allow and record randomisation and ability to collect specific tests and variables with minimal additional work
- Higher data quality and better coding procedures

5. Methods to control for confounding

- Confounding by indication and channelling of treatments are the main challenges
- Focus on methods to handle unmeasured and mismeasured confounding
 - Additional data, instrumental variables, propensity scores, disease risk scores, active comparators

5. Methods to control for confounding - conclusions

- Identify a subset of the observational study population that mimics the RCT and generate similar results
- Sensitivity analyses to test the robustness of study results
- Analyses challenging when
 - strong adherence to treatment guidelines makes allocation of treatment less random
 - prescribing tends to be highly selective immediately after marketing → disease risk scores
 - chronic conditions have time-varying exposures → marginal structural modelling

Priorities for EFSPi

- fast changing heterogeneous environment
- how to evolve science incl. statistics to answer relevant questions, RLE (Real Life Evidence), cost effectiveness evaluation etc.
- Challenging for statisticians brought up in a regulatory driven environment under ICH, FDA, EMA etc. to adopt to a very different environment with different questions and using information outside of RCT's



Questions

- What areas are a priority?
- What is the level of expertise/experience?
- What opportunities / challenges are we facing?
- Does EFSPI have a role and if so, what?

Survey

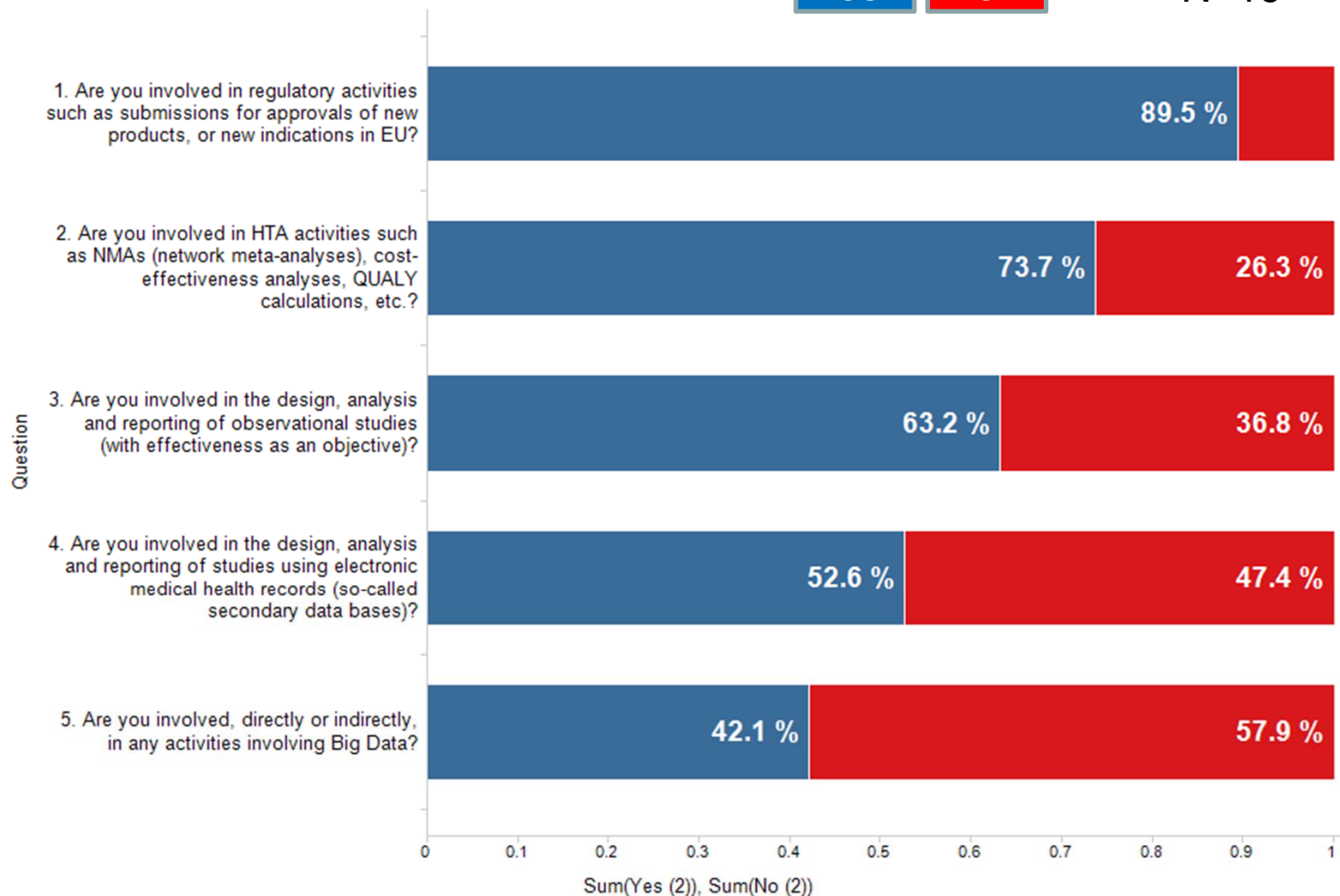
- Goal:
 - to get insight in level of involvement of Statistics Leaders in recent new developments
 - Input into discussion in Stats Leaders Mtg afternoon discussion
- Response Rate: $19 / 31 = 61\%$

Results Survey

Involvement in Recent Development (Yes/No)

Yes No

N=19



Involvement in Recent Developments

2. Are you involved in HTA activities such as NMAs (network meta-analyses), cost-effectiveness analyses, QALY calculations, etc.?



- NMAs, ITCs, Value Dossiers, QALY significant value
- NMAs: from design to interpretation; Cost-effectiveness Involvement: getting more and more involved from scratch to interpretation
- Supervision and coordination role for team members
- Statisticians sit on HTA core working groups and they are actively involved in the planning and development of HTA dossiers
- we have some key technical expertise in Bayesian methods/NMA and we're attempting to transition this to a more dedicated group
- general statistical support for questions the HTA unit ask. The plan is to take more proactive role in HTA and "push" statistical perspective to HTA activities
- The econometricians are in Biometric Division and they do all the statistical analysis for HTAs

2. Are you involved in HTA activities such as NMAs (network meta-analyses), cost-effectiveness analyses, QALY calculations, etc.?

73.7 %

26.3 %



- access to patient-level (competitor) data, NMA meta-regression best practice
- Need for increased expertise in NMA
- Fragmentation and quick changing landscape of standard of care
- to ensure that both authorities and our internal stakeholders understand the need for statistical expertise in HTAs
- choice of comparators for confirmatory RCTs - choice of endpoints in confirmatory RCTs - subgroup analyses and pre-specifying which ones are important for HTA with rationale - statistical methods for handling treatment crossover (time to event trials), quantifying uncertainty in effects and cost outcomes, network meta-analyses, extrapolating data beyond RCT, design and analysis of observational research studies
- The proliferation of very poorly understood and often biased statistical methods

2. Are you involved in HTA activities such as NMAs (network meta-analyses), cost-effectiveness analyses, QALY calculations, etc.?

73.7 %

26.3 %



- going beyond the QALY, integrating observational/trial data, properly incorporating sources of uncertainty, particular when extrapolating to situations where data may be lacking
- IQWiG methodology which asks for binary endpoints regardless what was measured in the study, means dichotomisation and therefore a loss of information and Power
- which methodological approaches to follow, how to choose comparators, how to handle different comparators for different countries, how to handle off-label use, how to handle literature search update to satisfy needs and different HTA submission times? Should the hierarchy of evidence be challenged: is a poorly designed, underpowered “Gold Standard” H-2-H RCT better than a well conducted NMA? Currently many HTA’s do not consider full networks and are only interested in an Indirect comparison in the absence of any H-2-H data. Ensuring that NMA’s that are submitted satisfy the methodological assumptions.

2. Are you involved in HTA activities such as NMAs (network meta-analyses), cost-effectiveness analyses, QALY calculations, etc.?

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- How do we introduce uncertainty into the models?
 - Software to conduct the economic modelling (i.e. EXCEL) is not sufficient to take advantages of improved methodology for conducting cost effectiveness modelling
- Defining Standard of care in the models
 - We often receive early advice from HTA's that the disease area is complex and previous models do not incorporate this complexity, but then we are also told that the models are too complex when they are submitted and review bodies are unable to replicate the results, either through lack of transparency of methods used, or the limitations of the software used.
- How to use efficacy results from RCTs to predict effectiveness in the overall patient population.
- How to handle the wish that each country desires local data QALY's
- biggest challenge is suitability of the EQ-5D for specific disease states.
 - it is shown that EQ-5D is insensitive to change in a number of different disease areas, the challenge is how to convert more appropriate quality of life measures, that can be compared with the EQ-5D. This issue might be: how to best collect the EQ-5D in RCT to fit the QALY needs i.e. is the "standard" collection at pre-defined time-points the best when a disease has not constant symptoms?

2. Are you involved in HTA activities such as NMAs (network meta-analyses), cost-effectiveness analyses, QALY calculations, etc.?

73.7 %

26.3 %



- The stats community can overcome and influence these challenges if they are part of the cross-functional teams supporting the planning and development of HTA submissions. Statisticians do have to consider a different perspective, that of the HTA decision maker, which is different to the regulator decision maker. Increasing earlier engagement and having a voice at the table to drive and influence HTA strategy is important for statisticians
- Broader methodological approaches are needed. To answer HTA questions, models tend to be more complex and relying on assumptions (more modelling). Statisticians should be trained more in complex modelling
- Need for increased expertise in NMA
- We have to challenge the rigor of analyses in this area and establish far better standards

3. Are you involved in the design, analysis and reporting of observational studies (with effectiveness as an objective)?



- We are a "platform" function and thus provide statistical support across research, development, Medical Affairs and HEOR
- Statistician as member of observational study team.
- Limited--technical consultancy to an epi group
- The econometricians are involved in designing the observational studies and responsible for data handling and analysis (mainly outsourced)
- My group oversee the majority of OR studies
- Statisticians are a core member of study teams and they are responsible for providing the statistical support required to design, oversee the conduct, analyse and report all observational studies retained in-house. Where the statistical deliverables (TFLs) are outsourced, the statistician would work with the vendor to ensure the planned analyses are completed to a high quality and help to identify additional analyses. The statisticians support all publication activities, including presenting results at congresses

3. Are you involved in the design, analysis and reporting of observational studies (with effectiveness as an objective)?



- Extent and limitation of data collection
- Reducing Bias is still an issue for CER studies. Collection of Patient reported outcomes can be time consuming, and puts into question the naturalistic aspect of these studies. Dealing with patient drop out and treatment switching is a common problem. A number of HTA's are now asking for post launch studies to assess real world effectiveness, need to develop designs and data sources which can do these efficiently. How do we demonstrate generalizability of these studies, and how do we compare efficacy from RCT's with effectiveness from Real World Data?
- Key challenge is to make more out of these studies than the "usual" marketing driven approach. But approaches like propensity scores in case of several treatment options are interesting and can add value in the interpretation and communication of results

3. Are you involved in the design, analysis and reporting of observational studies (with effectiveness as an objective)?



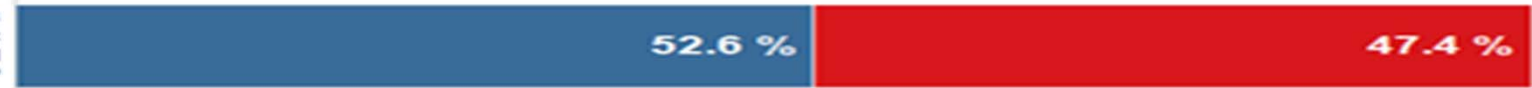
- main methodological challenge is around the control of bias and confounding.
- I don't see major challenges
- No specific challenges
- many & varied key challenges: combining efficacy with effectiveness, adjustment for treatment switching

3. Are you involved in the design, analysis and reporting of observational studies (with effectiveness as an objective)?



- we need to recruit and develop statisticians that are able and have interest in dealing with these challenges and broaden out from the normal RCT field
- Much more needs to be done to up skill people on methods, understand methodological properties

4. Are you involved in the design, analysis and reporting of studies using electronic medical health records (so-called secondary data bases)?



- Technical input to epi/related groups
- Involved in CPRD analyses
- Design, Analysis and Reporting of Drug Utilization Research studies through vendors
- The econometricians are responsible for data extractions and analysis of data (could be outsourced)
- Statisticians work closely with the epidemiologists to design and develop research proposals for existing database studies. Where the data can be brought in house, statisticians are supporting the analysis and reporting of the studies. Where there is no direct access to data, the statistician will be involved in the review of results via publication articles

4. Are you involved in the design, analysis and reporting of studies using electronic medical health records (so-called secondary data bases)?

52.6 %

47.4 %



- Suitability of the available databases (over 900 secondary databases). Considerable differences between EMR's and Claims databases, valid endpoints for effectiveness studies are generally missing or poorly recorded, and many assumptions have to be made. Consistency of results (e.g., case of papers published of two different researchers giving opposing conclusions on same question using same database)
- Key challenge is to really dig into what the data collected represent.
- Challenges in addition to observational studies, much more work around coding and missing data - particularly around missing not at random.
- Lack of awareness of its potential, poor data management

4. Are you involved in the design, analysis and reporting of studies using electronic medical health records (so-called secondary data bases)?



- Key challenge facing statistics is the lack of people with appropriate skills--need teams with computing/statistics/epi and sufficient knowledge of all these to communicate effectively. Keeping up with a fast moving field---need to have the right external/academic collaborations and be driving the agenda not following. Technically--confounding, particularly by indication. Key change--people, external involvement
- Key scientific challenges to understand how to use data collected for various purposes to answer questions outside the scope of collection. How to evaluate quality of the databases, the analyses and conclusions drawn.
- Quantity and standardization of data

4. Are you involved in the design, analysis and reporting of studies using electronic medical health records (so-called secondary data bases)?

52.6 %

47.4 %



- We as pharmaceutical statisticians are only starting to look at this
- A lot of work has been done to develop methods to address the bias caused by confounding factors, but less research has been done on all of the other types of bias that exists in using secondary databases. Need for structured and clearly pre-defined sensitivity analysis. From the more frequently used databases we need the owners to conduct research on their data to identify issues with bias within their database.

5. Are you involved, directly or indirectly, in any activities involving Big Data?



- Substantially in the 'omics' field, a little in HER
- Only to the extent that the work that we do uses "big data".
- Big data opportunities are under evaluation. I have a key responsibility about the next steps
- I am an Non Exec Director for the UK's ADRN - linking government data for public good
- In case also secondary data bases involving huge data sets are considered Big Data then yes, we have been involved
- Big Data is a buzz word these days. But with possibilities to access more and more information will become relevant for pharma statisticians to handle large datasets/databases such as those mentioned above
- We have a cross-functional 'Big Data' project running out of Biometric Division. The scope spans from Research through Development to Market Access (started 2014)

5. Are you involved, directly or indirectly, in any activities involving Big Data?

42.1 %

57.9 %

- Challenges: people, as above; risk the field will be dominated by computer scientists; hype leading to inflated expectations/claims, lack of infrastructure
- Concerns over identification of individuals, coping with EU legislation on consent, having clear proposals reviewed by independent approvals panel
- Key challenge is how to use the data if not collected and governing it yourself. The data structures can be very complex and the algorithms are not straightforward. It is not always "what you see is what you get".
- Some of the challenges are more around exploratory analyses, data mining and processing.
- Only to the extent of developing integrated internal data marts of RCT and observational research studies.



5. Are you involved, directly or indirectly, in any activities involving Big Data?

42.1 %

57.9 %



- Change: this need to be a core part of what stats groups do, and stats has to be acknowledged as essential to effectively work with big data, with corresponding implications for the above
- Transparency and development of proper methodology is needed
- Needs something of a mind set change to move towards hypothesis generation rather than testing
- This is a key area I think Pharma Statistics is generally not very engaged but where we should be. There will be an increase in the use of different technologies to collect health related data, and statistics are well placed to contribute to how this data is collected, analysed and reported to support advancing healthcare We should develop a SIG on Big Data to see what is emerging and seeking to identify the opportunities for statistics.

Priorities for EFSPI

Given these developments, what would be the Statistics Leaders group see as:

- preferred **priorities** for EFPSI
- **level of involvement** of EFSPI
- **focus** of EFSPI