



## **Select methods, toolset (such as the Janus program) and datasets to perform scenario studies in order to facilitate stakeholder's engagement**

August 2016

*The work leading to these results was conducted as part of the ADAPT SMART consortium (Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes). For further information please refer to [www.adaptsmart.eu](http://www.adaptsmart.eu). This paper is the result of the collective input from working group D2.04 and only reflects the views of the authors.*

*This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115890. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.*





## NEWDIGS NEW Drug Development ParadIGms Initiative

### ADAPTIVE DESIGN LABORATORY

Workshop Co-hosted by ADAPT SMART, GetReal, & MIT NEWDIGS

June 1-2, 2016

EMA Offices, 30 Churchill Place, Canary Wharf  
London, United Kingdom E14 5EU

### WORKSHOP SUMMARY

|   |           |
|---|-----------|
| <b>Day 1.....</b>   | <b>3</b>  |
| <b>Background to the workshop.....</b>                                      | <b>3</b>  |
| <b>Workshop Introduction .....</b>  | <b>3</b>  |
| <b>Objectives of the three consortia for the workshop.....</b>              | <b>4</b>  |
| ADAPT SMART.....  | 4         |
| GetReal .....   | 4         |
| NEWDIGS .....   | 4         |
| <b>The NEWDIGS Data Program Framework .....</b>                             | <b>5</b>  |
| Evidential needs.....   | 5         |
| <b>The MVET model .....</b>   | <b>5</b>  |
| Meaningful evidence .....   | 6         |
| Valid evidence.....   | 6         |
| Expedited evidence.....   | 7         |
| Transparent Evidence .....  | 7         |
| <b>The FDA's Sentinel Initiative .....</b>                                  | <b>7</b>  |
| <b>GetReal Case Study .....</b>   | <b>7</b>  |
| Why the different estimates? .....  | 8         |
| Potential utility of this approach .....                                    | 8         |
| <b>Unmet Medical Need .....</b>   | <b>9</b>  |
| <b>Encouraging real world evidence repositories .....</b>                   | <b>9</b>  |
| The EU approach.....  | 10        |
| Data quality and curation .....   | 10        |
| Funding mechanisms .....  | 10        |
| <b>Summary and next steps from Day 1.....</b>                               | <b>10</b> |
| <b>Day 2: Case study .....</b>  | <b>11</b> |
| <b>Gilenya and Multiple Sclerosis .....</b>                                 | <b>11</b> |
| Clinical Development .....  | 12        |
| <b>Simulation of Gilenya data .....</b>                                     | <b>12</b> |
| <b>What is the effect of the simulation on different stakeholders?.....</b> | <b>13</b> |
| <b>Impact of APs on patient safety .....</b>                                | <b>14</b> |

|   |           |
|---|-----------|
| Pragmatic trials .....  | 14        |
| Effect on safety .....  | 14        |
| <b>Integrating RWE into AP development plans .....</b>                    | <b>15</b> |
| <b>Workshop Conclusions.....</b>  | <b>15</b> |
| Considerations on best evidence .....                                     | 16        |
| Dealing with uncertainty.....   | 16        |
| The future? .....   | 16        |
| <b>Annex I: Design Lab Agenda.....</b>                                    | <b>18</b> |
| <b>Annex II: Participant List .....</b>                                   | <b>20</b> |
| <b>Annex III: SureReal Capabilities to inform AP and RWE designs.....</b> | <b>23</b> |

Organizational contacts:

IMI ADAPT SMART: André Broekmans, Director, Lygature, [andre.broekmans@lygature.org](mailto:andre.broekmans@lygature.org)

IMI GetReal: Sarah Garner, Associate Director R&D, NICE, [sarah.garner@nice.org.uk](mailto:sarah.garner@nice.org.uk)

MIT NEWDIGS: Gigi Hirsch, Executive Director, [ghirsch@mit.edu](mailto:ghirsch@mit.edu)

## Day 1

### Background to the workshop

To facilitate earlier access to effective medicines for patients with an unmet medical need is the goal of most stakeholders in the healthcare environment. However, although attempts to speed the process have been welcomed by several stakeholders, some believe that it will lead to an unacceptable lowering of standards and is merely a charter for the pharmaceutical industry to increase profits. Nevertheless, most stakeholders recognise that patients with life-limiting diseases, or other high unmet medical needs, may not have the luxury of time.

With a traditional development path, there is the so called “magic moment” when, after a positive regulatory and reimbursement/payer review, all patients within a particular indication have access to the treatment. However, within a particular disease area there will always be those patients where the potential benefit is much greater – for example, those with a rapidly progressive disease where treatment is either unavailable or ineffective. The rationale behind an earlier access approach for such patients with high unmet medical need is that a higher uncertainty relating to both safety and efficacy could be acceptable to patients with the most to gain and also to the other stakeholders in the process. Early access - with full disclosure of still existing uncertainties - is thought to be a significant step in offering the benefit of choice to these patients.

An early, limited, authorisation for a small well defined target population would be conditional upon a commitment to continued evidence generation to reduce uncertainties and consequent complete reviews as more evidence becomes available. Subsequent decisions could result in expanding the initial license with broader patient access to the product, in continuing restrictions or even product withdrawal – all depending on the nature of subsequent evidence and stakeholder deliberation. This approach, currently being evaluated through the ongoing European Medicines Agency’s (EMA) Adaptive Pathways pilot, is also known as Adaptive Biomedical Innovation or Medicines Adaptive Pathways to Patients (MAPPs). Adaptive Pathways (AP) will be used throughout the rest of this document but is used synonymously in this document with the other terms.

Another facet to the early access issue is that whereas clinical trials are the gold standard for proving efficacy, how a medicine performs when it is used by the much broader real world population under more variable conditions (effectiveness) may be different. In most situations clinical trials will be required for proof of concept but this early data could be supplemented by the use of real-world evidence to support the clinical trial data. The criteria for authorisation and reimbursement are different and the evidence of efficacy and a positive benefit-risk balance, which is sufficient for authorisation, may not be considered as providing enough evidence of effectiveness for reimbursement. The numerous stakeholders involved in developing, approving, prescribing, paying for and using medicines all have a stake in these decisions and the criteria used in making them.

### Workshop Introduction

The three consortia who took part in this workshop share common goals in looking for ways to achieve early access to medicines where there is an unmet medical need, and a desire to increase the role of real world evidence in the drug development pathway so that all evidentiary needs are satisfied. Each consortium has a different mix of stakeholders and varying objectives but the aims are similar. This report summarises the workshop, the presentations and subsequent discussion. Under the Chatham House rules, no attribution for questions or answers during the discussion is given.

## Objectives of the three consortia for the workshop

The consortia presented their main objectives:

### ADAPT SMART

- Enable different decision makers/stakeholders to express their views on concrete cases in a structured way.
- Identify issues related to evidence-access trade-off decision-making where there is a lack of alignment among stakeholders.

### GetReal

- Explore ways that methods of Real World Evidence (RWE) collection and synthesis could be adopted earlier in pharmaceutical development and the healthcare decision making process.
- Identify and characterize new approaches to decision-making support, including potential tools to allow for the evaluation of development programs and use in the assessment of the value of introducing new treatments.

### NEWDIGS

- Apply and refine the emerging NEWDIGS RWE qualification framework through its application to several retrospective cases within the context of an Adaptive Pathways/Adaptive Biomedical Innovation paradigm.
- Inform the ongoing evolution of the NEWDIG Scenario Design processes and tools.

The different types of uncertainty were discussed. There is always scientific uncertainty regarding safety and effectiveness, whatever the timing of authorisation, but this uncertainty is increased when access is granted earlier in the development pathway. Will this increased uncertainty lead to unacceptable risks to patients? An additional uncertainty is how the product will affect resource utilisation. It was acknowledged that uncertainty is not limited to “scientific” elements but needs to include “behavioural” elements relating to the different interrelated stakeholders as well. This behavioural uncertainty may include:

- Can early access in an Adaptive Pathway authorisation be effectively restricted to the initial limited target population?
- Is the required close monitoring/registries of patients in place? Are patients – on or off label – effectively included in registries and/or other follow-up data collection?
- Will all stakeholders fulfil their obligations as agreed and in what timeframe?
- Will a product that is being used by patients be removed from the market if the assumptions that led to access are shown to be false or insufficiently clear with the accumulation of further evidence?

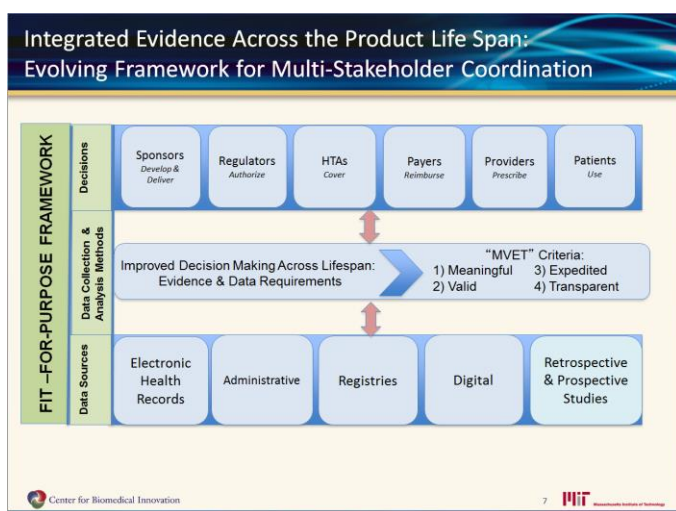
Both types of uncertainties will affect the success of early access ventures. This suggests the need for an Adaptive Development Plan which includes proposals for milestones for decision making when new evidence (scientific knowledge) and developments (behaviours) become available. It is likely that such a plan would need to be case-specific, but that some common elements will carry over between cases.

## The NEWDIGS Data Program Framework

MIT's NEWDIGS (**NEW** Drug **D**evelopment **ParadIGMs**) has, among its various initiatives, the Data Program. Throughout the life-cycle of a medicinal product, knowledge increases about the medicine and the uncertainties surrounding the estimates of benefits and risks decrease. The key decision along this continuum is at what point do patients get access to a product, and is a trade-off between expected benefits and risks (for licencing) and expected relative cost effectiveness (for payers). AP aims for earlier access on the development pathway for a specific target population, with the greatest unmet medical need, based on the understanding that a specified, adaptive pattern of research will continue which will lead to a decrease in uncertainty and, with positive evidence, a likely broadening of the indication.

Implicit within this understanding of uncertainty is that subsequent evidence may show that the benefits are less and the risks more and that decisions may need to be reassessed. This is not a failure of the system but an inherent part of managing uncertainty. Each stakeholder needs to understand the uncertainties at the time of initial access and how it affects them - and other stakeholders.

### Evidential needs



Different types of evidential needs may be addressed by different types of studies (randomized controlled trials, non-interventional studies such as registries; databases of various types, etc.) The study type, and its conduct, should meet the needs of the stakeholders and thus be “fit-for-purpose.”

Certain stakeholders have an inbuilt bias towards particular forms of studies. For example, for regulators, proving efficacy usually depends upon randomised controlled trials (RCTs). Randomisation controls many forms of bias so any difference seen between

a product and its comparator is assumed to be due to the effect of the drug. Non-interventional, or observational studies, do not employ randomisation so other methods are needed to control for confounding and bias to allow confidence in the results.

Decisions on an AP approach and the consequential adaptive development plan need to be made acknowledging these different evidential needs. The importance of the NEWDIGS approach is that multiple stakeholders work together toward developing solutions to reduce important uncertainties and satisfy all evidentiary needs.

Although the questions, evidence and decision points, for each product may be unique, the aim of NEWDIGS is to examine multiple cases and extrapolate knowledge from each to build a standard set of high level criteria to decide at each stakeholder level what the key questions are and the most appropriate methods and data sources to answer each question.

## The MVET model

One of the core principles around AP is the use of RWE to supplement that of randomised clinical trials. Robust approaches to performing clinical trials developed over 70 years and cumulated in a set of standards known as Good Clinical Practice (GCP.) These standards mean that evidence from RCTs is generally regarded as trustworthy - although its applicability to the wider patient population may be limited. Pharmacoeconomics is a much newer science and the ability to control for confounding and bias has really only been developing over

the last 30 years - along with the rise in computing power to handle the much more sophisticated analyses needed. Early failures to control for confounding and bias led to results which were later shown to be invalid leading to some people having concerns about the evidentiary robustness of RWE. Standards have, and are, being developed for observational research, but choice of study and analysis methods are still key.

Much pharmacoepidemiologic database research involves the secondary use of data collected for other purposes – typically clinical, prescription or claims management. De-novo primary data collection collects specific data on the subject of interest and can be targeted at specific exposures or diseases or be used to supplement data from databases. The MVET framework (middle of figure above) for observational studies is designed to ensure that the right evidence is generated at the right time. The MVET framework is defined by characteristics of evidence:

1. **Meaningful evidence**
2. **Valid evidence**
3. **Expedited evidence**
4. **Transparent evidence**

### Meaningful evidence

How well do the data sources assess the exposures and outcomes of interest? How well are confounders, or proxies for confounders, assessed and addressed? Are there biomarkers or other indicators available and accurate enough to identify the target population for highly targeted therapies? Can the data be linked to other databases or primary data sources? What is a meaningful comparator? Can data or analyses be pooled?

In the context of Meaningful Evidence, three sources of data were discussed along with advantages and concerns.

Claims databases – reflects routine care of patients and is fairly complete for major clinical outcomes, resource use, costs, but lacks detailed clinical data and Patient Reported Outcomes (PROs)

EHRs (electronic health records) – tend to have more clinical data than in claims databases, but frequently have missing data and no PROs

Disease registries – more likely to have PROs and specific clinical outcomes, but have limited availability and are time consuming to initiate.

### Valid evidence

Validity refers to the idea that study designs are employed appropriately along with “bias reduction methods to support causal interpretations of effectiveness estimates”;

The study design should aim to avoid or reduce bias to enable causal interpretation. Study design also needs to reflect what the evidence need is.

1. Purpose – confirming initial indication or extending indication
2. Condition - characteristics of the disease of interest (monotonic progression or episodic)
3. Therapy - timing of the therapeutic effect eg rapid onset or incremental effectiveness
4. Stakeholder– e.g. effectiveness, safety, utilisation, cost or value.

Other factors which impact the study design include: what is known about the natural history of the disease; numbers of patients affected; timelines of evidence need; logistical constraints and data availability. It may be difficult to pick an appropriate comparator if there is very rapid uptake of a new treatment which is highly effective, since less effective treatments may be dropped. Choice of treatment may depend upon the severity

of the disease or clinical guidelines. In some circumstances it may be possible to use a patient as their own control – ie pre-post treatment but this requires a predictable uni-directional disease course, otherwise incorrect inferences may be drawn e.g. where patients get worse or better due to the natural history of the disease independent of any treatment. There may also be occasions when confounding and bias cannot be controlled and randomisation is essential

### Expedited evidence

The degree of uncertainty may influence the urgency for evidence and hence data source, with a balance between speed and not compromising validity. Initial concerns over lack of information on the safety profile may drive close monitoring of an initial exposed population. In other cases, embedding data abstraction into a data stream with rapid cycle analytics may allow cohorts to build over time with incremental analyses leading to a reduction in confidence intervals around a point estimate. Decision makers need to understand how to interpret evidence rapidly since new data may arrive frequently.

### Transparent Evidence

The evidence generator is usually a different person from the decision maker so the decision maker needs to trust the evidence. Trust involves understanding how the evidence was generated, the assumptions underlying the chosen parameters and the ability to reproduce the same result. Therefore audit trails of data preparation and analyses and complete process transparency may prevent distrust of differing results from the same data source.

Discussion suggested that the M and V criteria were likely to be context-specific but that E and T could largely be standardized.

## **The FDA's Sentinel Initiative**

The Sentinel program is an example of RWE in practice. Born out of the 2007 FDA Amendments Act, which required the FDA to establish a system to link and analyse safety data from multiple sources, it is a distributed network which collects data from 18 different healthcare systems covering more than 193 million people. Piloted as Mini-Sentinel, the full system transitioned and was formally launched as "Sentinel" in February 2016. The person-level data is held locally in centres or "nodes" where analyses are performed with results being sent to a central hub and pooled. This model overcomes some of the difficulties over data protection and avoids transfer of un-anonymised data. The validity of this model was tested by comparing pooled results from analyses done in 3 local nodes with results of analyses using the combined data set. There was no difference.


The most important node attribute is clinical understanding of how the data is generated as this must be captured and will be node-specific. This understanding is needed to structure the node's data in an appropriate Sentinel format so that no mapping is needed for analytic capabilities. Nodes do not need people with programming ability since centres can download SAS code. Which nodes to use for each set of analyses goes back to the "meaningful" part of MVET and will depend on the population of interest and the coverage of the individual healthcare system. Different healthcare systems may have different medical treatment patterns or be subject to cultural differences. Since pooling of results requires homogeneity to some extent, data from outliers may need to be treated separately. In theory, in the US, the FDA could go back to the nodes to audit data or see how individual results were generated.

## **GetReal Case Study**

One of the criticisms of clinical trials is that the patients in them are often not typical of the patients found in the real world – one aspect of the efficacy/effectiveness distinction. The aim of this case study was to mimic

the real world population of non-small cell lung cancer (NSCLC) in a model using clinical trial data. Data from two studies comparing cisplatin plus either gemcitabine (C+G) or pemetrexed (C+P) as first line treatment were used. One was a phase III RCT and the other an observational (real world) study. In the Phase III study, patients on C+P had a median survival time of 11.8 (95% CI 10.4-13.2) compared with 10.4 (95% CI 9.6-11.2) for the C+G group. In the observational study, C+P had a median survival of 11.6 (9.9-14.4) compared with C+G of 8.4 (6.7-10.8). The interventional study showed a C+P median survival advantage of 1.4 months compared with 3.2 months in the observational study.

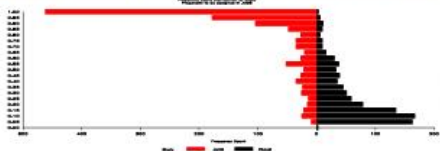
### Why the different estimates?




## Propensity weighting

Real-Life Data in Drug Development

- Propensity score model **predicts participation** in either RWE or RCT, given a set of covariates (RWE and RCT data are pooled for that purpose)
- Resulting propensity scores are used to
  - quantify the difference** between the two cohorts, and
  - match, subclassify or weight the RCT outcomes** to the RWE population
- „Classic“ propensity scoring often used to mimick RCT in RWE setting. Here, propensity scoring is used to mimick RWE in RCT setting.



- Prior to launch, **only baseline RWE information needed** to assess RCT outcomes under RWE conditions



The research leading to these results has received support from the Innovative Medicines Initiative (IMI) under grant agreements (101019755 and 101019756) which are co-funded by the European Union and the European pharmaceutical industry.

Programme (IMI) 101019755 and 101019756 are co-funded by the European Union and the European pharmaceutical industry.

IMI 101019755 and 101019756 are co-funded by the European Union and the European pharmaceutical industry.

Defining WPI Case Studies  
MC 02 June 2015 Slide 27

Propensity scores were used to predict participation in either the RCT or real world study given a set of co-variables and it became clear that very different patient types were included in each study. This is typically the case with RCTs being less representative of a potential real world population since they are trying to reduce variance in order to facilitate statistically significant findings. Based on propensity scores, inverse weightings were applied to data in the RCT to attempt an adjustment for patient type. In this manner the trial results were re-weighted to represent the mix of patients in the real world of NSCLC treatment.

As an example, 81% patients in the observational study had 0-1 metastatic sites versus 24% in the RCT. Applying weights to the RCT suggested that the median time to death, which increased by one month in the RCT in favour of pemetrexed, would increase to 5 months in the real world population if they had the same adherence and behaviour of the RCT population. This suggests that the results of the drug in the real world will be better than predicted from the RCT. However, the base case of the re-weighted analysis also showed an increase in the HR. However, a single HR is only reliable if the survival curves remain parallel over time which is possibly not the case in this example

A number of other results were examined in a sensitivity analysis with broadly similar results. In this example, treating patients at an earlier stage of disease progression (0-1 metastasis) led to better results in the C+P group. This methodology of identifying “benefit factors” could be used to steer treatment to those most likely to benefit.

### Potential utility of this approach

Using RW weightings on RCT data could also be used to measure risk factors in different sub-populations. An important point emphasised during the discussion was the necessity of considering difference measures when looking at benefit or risk in a heterogeneous population. For example, relative risk is not affected by variations in baseline rates across the subpopulations whereas a risk difference is. Consider a relative risk increase of 20%. If the baseline risk in a subpopulation is 50 per 1000, the increased risk will be 60 per 1000 or a risk difference of 10 per 1000. If the baseline risk were 5 per 1000, in this population the increased risk will be 6 per 1000 – a risk difference of 1 per 1000. For a patient with 5 metastases the risk of death is different from someone with 1 metastasis and, while the *relative* benefit from a treatment (vs. other or no treatment) may be similar between such patients, there will, nonetheless, be different *absolute* levels of benefit.

By measuring the characteristics of the target population one can predict how the drug will behave in the real world. Budget impact models could be built to see how the drug will behave in particular populations with particular characteristics. It could also be possible to use the results and weighting of phase II trials to influence

the population of phase III trials. However, seeding trials with patients predicted to benefit may lead to concerns over the plausibility of effect estimations across the target population.

This example demonstrates differences between RCT and real world populations. An RCT is designed to prove efficacy and may not be predictive of effectiveness in the real world population. This methodology provides a means of combining evidence from both worlds. However, there may be difficulties in deciding what the target real world population is in the absence of an indication for the drug and it requires knowledge of the epidemiology of the disease. There was also doubt whether modelling would be considered sufficient as an evidence basis but could be beneficial in identifying the “right” population to treat as compared with the population studied in the RCT.

## Unmet Medical Need

What is meant by unmet medical need? Traditionally it is thought to be those diseases where there is currently no effective medical treatment. However, even in diseases where there are multiple effective treatments, there may be patients who do not benefit or for whom benefit is minimal, leaving substantial unmet medical need. In addition, a disease may have treatment but there is an unmet medical need in relation to a particular symptom. For example, in multiple sclerosis, fatigue is a major issue and can have a huge impact on the ability to remain or become employed, yet current treatments often fail to adequately address fatigue. As a consequence there is still an unmet need in controlling fatigue and a continuing personal and societal cost of the disease. Patient input is desirable into deciding what outcomes are meaningful and where there is unmet medical need.

Rare diseases by definition have a limited number of patients who might benefit from a drug. With ultra rare diseases, traditional drug development may not be economically viable. Would it be possible to bundle together indications where a promising treatment is expected to work for all of them? For example a gene therapy may have proof of efficacy in one indication and an understanding of the mechanism shows that it will be effective in a different indication with a similar genetic cause. The problem is whether certain stakeholders will allow extrapolation from one indication to another. One of the stumbling blocks to this approach is that payers do not provide advance specifications for a drug but, rather, have to buy the drug (or not) as developed. Companies tend to develop drugs based on economic considerations – as public companies with shareholders they need to provide a return on investment. Real world evidence could be used to guide product development by understanding evolving targets and unmet patient needs and form the basis for discussion on what would be a meaningful outcome.

## Encouraging real world evidence repositories

There are divergent views regarding the value of real world evidence which needs to be addressed. Demonstrating that it can produce good insights, and that good science can be done with real world databases, is important to help address the concerns of stakeholders. Also important is a continuing recognition that RCT evidence has its own limitations, perhaps not in the traditional realm of efficacy determination – the focus of licencing decisions - but in the worlds of other decision makers, including providers, patients and payers. RCTs, with protocol-driven actions and perhaps unrepresentative centres and providers, may be less suited for real world prediction. As RCTs are recognized as sometimes having limited predictability of RW effectiveness, and might not always provide meaningful evidence to address certain questions, supplementing and integrating RCT evidence with RWE may be needed. However, work is needed to provide a better understanding of the value of this approach without which large scale investment is unlikely.

Currently RWE is often requested post-authorisation, but it might be possible to do some of this research in the pre-authorisation environment.

### The EU approach

In Italy, data collection is the basis for the final agreement on price with the real world evidence providing the evidence of the real value of the drug when the price is re-negotiated after 2 years. This requirement is a specific mandate in Italian law and has resulted in 125 registries. However this places a burden of work on doctors and physicians and there is a need to simplify the workload so they are committed to enter data. It is possible that a standard methodology would help with this, but data collection is frequently on a case-by-case basis. The European Medicines Agency (EMA) has an initiative aiming to leverage registries across the EU. Ideally high quality registries should be created in advance by developing infrastructure at the national level. Pharma could contribute to this through public-private partnerships but the structure should be sustainable. A partnership of stakeholders could discuss what a good registry would look like in a particular disease area – so that all stakeholders may achieve their goals. The problem is that registries should be set up to answer specific questions rather than just collect non-specific data. Moreover, as each stakeholder may have different emphases on the data it seeks, the specific questions need vetting in a multi-stakeholder environment. If a multi-purpose registry is wanted, one needs a broader data collection effort which is then burdensome and may still not answer certain questions. There is a trade-off between data specificity and broader use.

Sentinel works because the data exists in the USA and is already being collected for different purposes. In the EU, the technological challenge is much greater to build the infrastructure because of widely different health care systems between countries.

### Data quality and curation

Data collected from normal medical practice will inevitably be incomplete and may contain mistakes so there is a question of curation. Some providers make provision of data a condition for reimbursement and data quality standards could be incorporated into this. There probably needs to be more research into the quality and completeness of different data sources.

### Funding mechanisms

Funding of registries will only happen if there is evidence that the evidence generated is of real value for decision making. Continuing to build “one-off” registries is probably not sustainable, unless the infrastructure for providing data is there. Stakeholders need to find more ways to work together to decide what constitutes “good” as far as a registry is concerned and also how to fund.

Discussion of possible funding measures for data collection included

- Public-private partnerships
- Tax on industry or other stakeholders (e.g. use part of co-pay amount)
- Linking provision of data by hospitals to reimbursement by payers
- Tax on users of data

One of the issues facing the EU is that under data privacy laws, data collected for one purpose cannot be used for another without the agreement of the person about whom the data were collected.

## **Summary and next steps from Day 1**

At one level there is progress: for example, real world data is already being used with single arm trials using the natural history of the disease as a control. Conditional licenses are given and data is then generated post – authorisation to lead to a full licence. However, it is difficult to extrapolate from a few examples into policy. The GetReal project will finish shortly and as part of its final report will produce recommendations. It will have

some good ideas, but the problem is sustainability and how to move on. We have a situation which is everyone's problem but no-one's responsibility to solve.

What is desirable needs to be broken into small steps which are achievable. We should aim to choose the best ideas and crystallise them into tangible steps to move forward to the next. Another possible way forward is by Darwinian selection – find 2-3 cases where adaptive development has led to an early payer's decision and utilisation on the market. Once this has happened and become show-cased, it becomes the norm as others will have an incentive to try a similar route. We should start with identifying important pre-competitive areas such as natural history registries.

The way forward may be for stakeholders to use areas of agreement as stepping stones and then build upon them. If we get people together and take the first steps and the concept works, then others will follow as their incentives may change with initial successes. A suggestion was made that "we don't need everyone; we need leaders and good examples."

---

## Day 2: Case study

Day 2 was largely devoted to a case study for an already approved medicine (Gilenya in multiple sclerosis) to simulate what might have happened if an AP approach had been used. Would patient access have been enhanced and with what implications for patient safety? One of the concepts behind AP is that the initial targeted subpopulation is that of greatest need and the indication then gradually expands, if appropriate, to include wider populations as more evidence on benefits and risks becomes available. The simulation exercise asks could an AP approach:

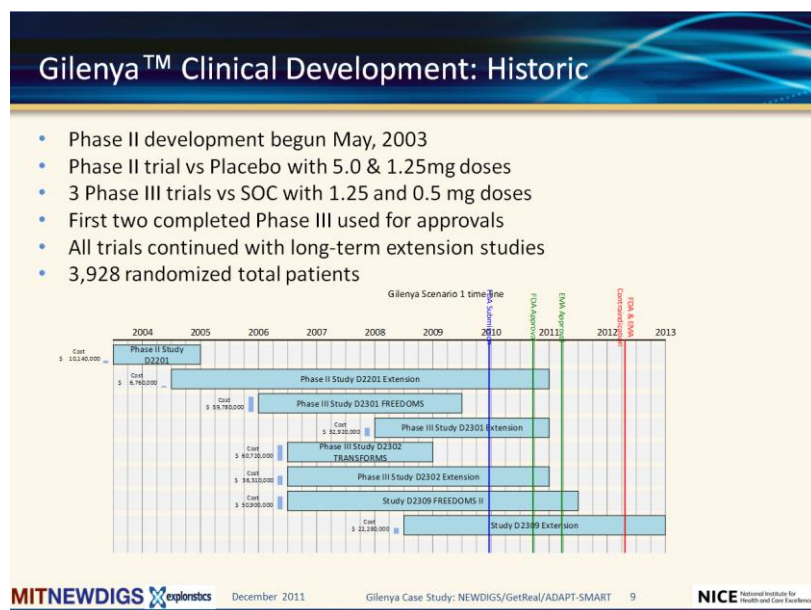
- Apply to a therapeutic medicine appropriate for an "All Comers" (broad population of patients) population as the Gilenya case appears to represent?
- Impact the number of patients exposed to a safety risk before it is identified?
- Employ evidence from pragmatic trials?

## Gilenya and Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease which results from an immune attack on axons leading to inflammation, demyelination and oligodendrocyte and neuronal loss. Although there is recovery in function between episodes (relapsing-remitting) the degree of disability progresses throughout the course of the disease. In general it tends not to be the severity of the individual attack which leads to disability but the frequency with which they occur.

Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator which blocks the capacity of lymphocytes to egress from lymph nodes. Its mechanism in MS is postulated as reducing the infiltration of pathogenic lymphocyte cells into the central nervous system thus preventing nerve inflammation and nervous tissue damage. There is no biomarker for identifying subpopulations and Gilenya appears to be uniformly efficacious across the disease spectrum making it atypical of the normal AP candidate medicine. Its main adverse effects are bradycardia, hypotension (particularly after the first dose), infection (including opportunistic) macula oedema and decreased pulmonary function.

## Clinical Development



Its clinical development, and subsequent events are illustrated in the adjacent figure. The first 2 completed Phase III trials were used in the marketing authorisation applications. It was approved in the US on 22<sup>nd</sup> September 2010 and in the EU on 17<sup>th</sup> March 2011. In December 2011 there was a sudden unexplained death in a patient within 24 hours of the first dose which led to a safety review (and Article 20 referral in the EU) of all cases of sudden/unexplained deaths and all cases of life threatening arrhythmias and conduction disorders. This

resulted in recommendations for more stringent monitoring after the first dose, and educational material (EU) and warnings/contraindications regarding use in patients, with a history of certain cardiac problems, or on medications which could potentiate the bradycardia or arrhythmic properties of Gilenya. By November 2015 approximately 285,000 patient treatment years had been accrued.

## Simulation of Gilenya data

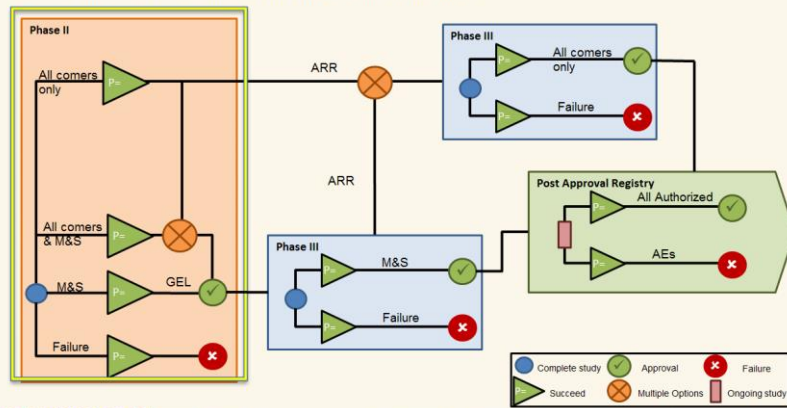
Modelling used the Kerus CT simulator, developed and licensed by Exploristics, and SureReal, part of the NEWDIGS Janus toolset developed by NICE and MIT NEWDIGS, to design potential alternative development scenarios with simulated decisions using only the information available at the time of development. Slides showing the capabilities of SureReal are included in annex 1.

The first phase of the simulation set out to replicate the sequence of the original development plan using the numbers of patients in the clinical trials and different simulations of the market share to match the 285,000 patient treatment years actually arrived at by November 2015. These showed a close match between the simulation and reality. The model also predicted accurately a number of other metrics – e.g. company revenue.

Since there is no known biomarker for predicting a higher responder population and Gilenya appears to be equally efficacious across the disease spectrum, an assumption was made that those with moderate to severe disease (M + S) would have a higher tolerance for risk as they have a higher unmet medical need. AP simulation modelling assumed that this group would be the target for an initial licence with later expansion to the all MS population, called “All comers” in the slides. The model also assumed that a registry would be set up for all patients receiving marketed drug and that access would initially be restricted to the M+S subpopulation.

## MAPPs Phase II Design Explores Putative Sub-Population And Creates Options

- Tests both Allcomers and Moderate & Severe (2 doses) efficacy via 6 mos GEL and 12 mos ARR
- Enables pursuit of both or either for pivotal trials
- Interim Moderate & Severe Ph III results can inform Allcomers



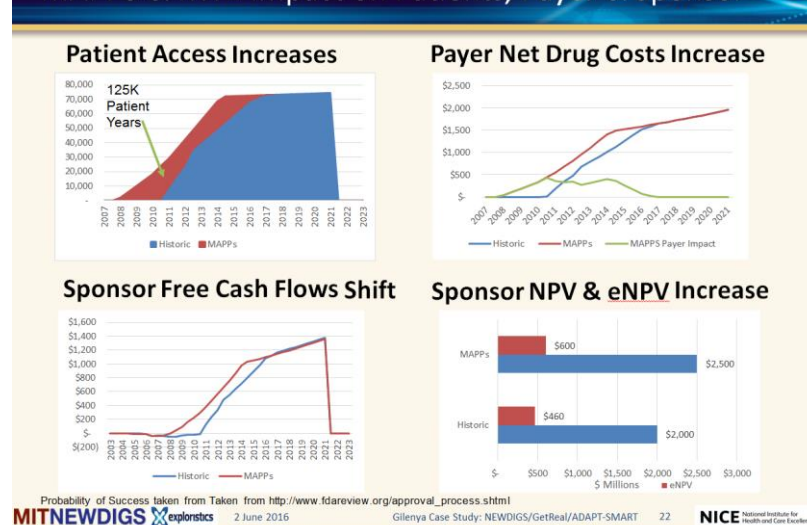
This diagram shows the possible outcomes (and subsequent development options) of a phase II trial in MS with either All comers only, the M+S subpopulation only, both populations or none showing benefit. Phase II was designed to give the same GEL (gadolinium enhanced lesion – a marker for disease progression) results as were found in the historic development plan.

The simulations designed the trials based on what the historic team did (or could) know at that point but simulated the results based on current knowledge.

The final simulated AP development plan allowed for 2 populations, moderate + severe (M+S) and “All MS.” In this alternative development plan, there would be 4 core studies, 4 extension studies (2+2 in each population) and a registry starting at the time of the initial M+S authorisation and continuing after the wider approval. Submission for the M+S indication would occur mid 2007. Submission for the broader all MS submission would be in 2010. The efficacy endpoints were gadolinium enhanced lesions (GEL) and Annualised Relapse Rate (ARR) and the safety endpoint was bradycardia. By increasing the Phase II study size from 240 (historic) to 450 (simulation), the AP pathway would show an 88% decrease in GEL. Phase III results in the simulation show a 60% decrease in ARR. Both phases II and III compare treated patients with placebo. Kerus predicted a 100% likelihood of success in finding both sets of results based on the trial designs employed since the results were greater than the estimations used in the historic trial designs.

### What is the effect of the simulation on different stakeholders?

## MAPPS & RWE Impact on Patients, Payer & Sponsor



The simulation predicted that an initial authorisation for M+S patients would occur in 2007 with the full MS licence at the observed historic time point (i.e. no change in timing for the full indication). This would increase patient access leading to an additional 125,000 patient treatment years by 2015. The effect on different stakeholders varied. The cost to payers is initially increased (because of earlier access) but the increased cost of AP over historical development becomes neutral around 2017. This model did not factor in the economic and societal gain of treated patients

being able to work.

Depending on assumptions, the sponsoring company metrics may be improved or decreased (i.e. there was no clear automatic “win” for the company under an AP approach). The potential effects on different stakeholders will change depending upon competitors in the market, the differing effects of earlier access, market share, competition with generics, exclusivity period, etc. which were not built into the current model. The suggestion was made that instead of product level simulation, one might need therapeutic area simulation to account for interdependencies of multiple company and other stakeholder actions. A major accomplishment of the model was its result that one need not have a biomarker to indicate a subgroup appropriate for an AP approach. In this case, the subgroup was identified by disease severity and an expected higher net benefit from treatment.

## Impact of APs on patient safety

There is concern that AP could result in some patients being exposed to greater risk because of increased uncertainty. In the Gilenya case, bradycardia and conduction defects had been identified as safety concerns during the clinical trial period, but patients with significant cardiovascular disease had been excluded from trials. Because of the 1<sup>st</sup> dose bradycardia and conduction effects, warnings and a recommendation for monitoring for a minimum of 6 hours after the first dose was included at initial authorisation. In the US, Gilenya was subject to a Risk Evaluation and Mitigation Strategy (REMS) and in the EU, educational material for physicians and patients was required to manage risks.

The simulation explored whether the increased risk due to prior cardiovascular history could have been detected earlier. In particular, it examined the probabilities under various AP scenarios of detecting this risk prior to the time of the observed death that occurred in December 2011. The incidence of cardiac arrhythmias was estimated as 4.5% in the MS population. The modelling assumed that the relative risk in patients with a history of cardiac arrhythmias was 10 x that of MS patients with no history of cardiac problems. If all patients were entered into a registry and provided a complete medical history, a signal was likely to have been detected at 6 months. With only 75% of exposed patients in a registry and only 50% with a complete history, the lag time for a high probability of risk detection is 12 months increasing to 15 months if the capture rate is only 50% for both parameters. This suggests that there was no increased risk to patients because the signal would be detected, and a contraindication put in place, before the expansion of the target population to the wider MS population. Those initially exposed are those most likely to benefit from earlier treatment so the benefit/risk balance could actually improve with this modelled AP approach. Although the number of patients in the modelled RCT population is fewer, the added registry in the case study would have enabled safety concerns to be identified at least as quickly as with spontaneous reporting after a conventional development and authorisation approach.

### Pragmatic trials

The modelling also looked at whether a pragmatic trial prior to the wider indications being granted would have detected the risk factors for bradycardia. The likelihood of detection in a pragmatic trial is dependent upon the rate of patient recruitment. The detection at 6 months in an ideal registry is only approached by a pragmatic study with recruitment of at least 170 patients per month. Assuming a 30 months study, a pragmatic trial of 3000 patients is estimated to cost \$60 million compared with \$13.5 million for a registry of 9000 patients. Discussion included suggesting that any deficiencies of a registry compared with a pragmatic trial might be remedied by additional expenditure to optimize the registry given the significant differences in budgets required. Also discussed were various strengths and weaknesses of both choices

### Effect on safety

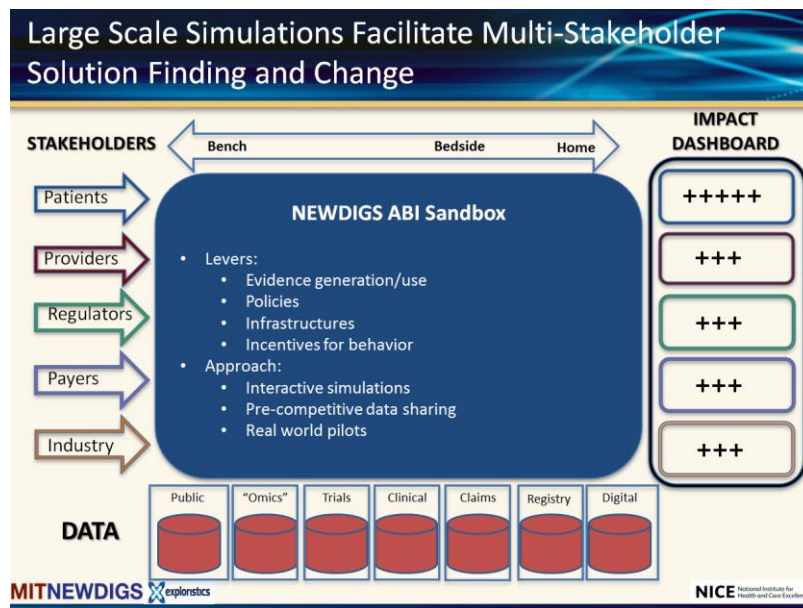
Discussion on this topic raised the issue of whether a registry was needed to identify such a risk or whether conventional monitoring might suffice. Monitoring to pick up safety signals need not be restricted to a registry only – other monitoring is available and could have contributed to identifying the signal.

In this case, bradycardia was a known risk so the identification of risk factors would be the key aim of follow-up. In other cases, it is important to pick up signals of new adverse reactions as early as possible. The data suggests

that in this example the AP would probably pick up signals earlier than could be done using the traditional development plan.

## Integrating RWE into AP development plans

There was considerable discussion on the relative benefits and costs of RCTs, pragmatic trials and real-world evidence including registries and “big data”. Each has advantages and disadvantages so the mix will depend upon what question is being answered and multiple sources of data may be required. Classical thinking suggests that efficacy needs to be answered with RCT data but observational data is often useful for identifying an increased risk. Observational studies are accepted as a means of identifying risks but can the converse apply? Would observational studies be accepted for identifying a decreased rate of an effect – i.e. a reduction in heart attacks? If acceptable this suggests that observational data could be used to determine efficacy. There was no consensus on this with the feeling that in many cases, the potential for selection bias would prevent firm conclusions being made?



Simulation allows generation of a large number of trials using different criteria and simulating individual level patient data. This can facilitate multi-stakeholder solution finding - particularly when combined with solid data. Impact dashboards (such as the NEWDIGS prototype shown here) can show the effect of changing parameters on all stakeholders. Simulation might help set trigger points for efficacy or safety if potentially contentious.

If there is a very small potential trial population or disease progression is slow, could

simulation replace clinical trials and are RCTs needed? When the number of available patients is very small, observational data may be acceptable – e.g. if the natural history of a disease is well characterised and predictable, then one may not need RCTs.

The economic effect of AP was discussed. Traditional development programmes for rare diseases are similar in cost to those for much larger target populations. As a result, market pricing of treatments per person treated is much greater for rare diseases to recoup development costs. Would using AP allow the development of drugs which would otherwise not be cost-effective by reducing costs and allowing earlier return on investment?

## Workshop Conclusions

Much discussion throughout the workshop, focussed on how best to ensure generation of the right evidence for the right stakeholder at the right time. There are many different stakeholders, with different questions and decisions to make, but these stakeholders are not acting in isolation. Whether big data, such as found in Sentinel, can be used or bespoke observational studies/registries are needed will depend upon the disease, the medicine and the intended target population. The MVET model provides a useful framework for assessing the value and suitability of different sources of observational data in decision making.

### Considerations on best evidence

It must be recognized that all studies (including RCTs) have strengths and weaknesses and accurate answers to many important questions may need to come from combining multiple types of studies. We should reconsider whether the biases due to non-randomisation in observational data are always that much greater than the biases introduced with a homogenous trial population and confounder cleaning. What is important, is to use the best study design to answer the particular question and a particular question may necessitate combining different types of evidence.

The Non-Small Cell Lung Cancer example from Day 1, provided an illustration of the value of modelling RCT outcomes using RWE to make it more generalizable (from the patient mix point of view.)

Integrating evidence from different sources is key to satisfying different stakeholder needs which need to be considered over the entire life cycle of a product. Real world evidence is important and the infrastructure to study disease epidemiology and relative effectiveness of medicines needs to be developed whether these be registries, healthcare system databases or other sources of evidence.

### Dealing with uncertainty

Some uncertainties may be simply not worth resolving. Criteria must be developed to decide which are critical. The costs of developing evidence need to be balanced with the specific need for that evidence. There are alternative means of reducing uncertainty – each with its own level of precision and cost. Depending on the precision needed and the costs, some methods may be better than others in addressing existing uncertainties. There may be a balance point when one has to just accept remaining levels of uncertainty.

Simulation was shown to be a powerful tool that can be used to model the effect of changing different parameters including economic models and clinical trial design. The effect of changing parameters on the needs of different stakeholders can be estimated to help optimise clinical development programmes.

The Gilenya case study demonstrated that increased monitoring of patient safety under APs may improve the detection of possible safety events. In the Gilenya example, the use of real world evidence as part of a AP approach may lead to increased efficiency, safety and cost saving. An important question regards its generalizability. The bradycardia risk was known early on and the observed death could have occurred at any time (month 1, month 24, etc.). In this case, the alternative development pathway shows quicker identification of this risk, but this may be only because the realization of the risk – the observed death - in the conventional development program occurred as late as it did. Thus, while this is an important case, illustrating (against general expectations) the potential for an AP approach to increase safety, it is not proof that an AP approach can succeed in this regard generally.

It also suggested that AP can be used in situations when there is expected uniform efficacy across a disease and where biomarkers for patient selection do not exist. It may be acceptable to use patients with the greatest potential for benefit to generate data about the benefits and risks prior to use in the wider population since the ability to detect signals is probably not inferior with AP and sometimes may be superior.

### The future?

The current model of drug development and subsequent pricing may not be sustainable with the move towards increasingly specialised therapies used in ever smaller patient populations. Using real world evidence at a much earlier stage in the development plan along with simulation and adaptive designs may lead to increased efficiency and a reduction in development time and costs.

The need to balance access to medicines against knowledge about the potential benefits and potential risks of a medicine will always lead to divergent opinions. There is no “correct” answer and individuals will have different approaches according to their situation, experience and approach to risk. The viewpoint of a dying patient with an unmet medical need regarding what is an acceptable risk may be different from that of a regulator or other stakeholder. There needs to be compromise from all stakeholders with an appreciation of

the different viewpoints and pressures. There also needs to be an understanding amongst stakeholders that the actions of one may have effects on several others and overall a better understanding of their interrelationships and interdependencies. There was widespread agreement that we need to consider a range of options, explore different ways to meet all stakeholder needs and work on areas of agreement so that we can increase the choice for patients.

## Annex I: Agenda

### Day 1: RWE First, not Last

Facilitated by Mark Trusheim - MIT

|               |  |  |
|---------------|--|--|
| 9:30 – 10:00  | Networking & Coffee  |  |
| 10:00 – 10:30 | <b>Welcome, Background, &amp; Introductions</b>  | Hans-Georg Eichler - EMA<br>Sarah Garner - NICE<br>Gigi Hirsch - MIT NEWDIGS           |
| 10:30 – 11:00 | <b>Setting the Stage</b> <ul style="list-style-type: none"> <li>Brief Introduction/NEWDIGS Data Program Framework</li> <li>Proposed framework for integrated evidence plans that are 'fit for purpose' (the "MVET model")</li> </ul> | G. Hirsch<br>Sebastian Schneeweiss – MIT NEWDIGS Data Program & Harvard Medical School |
| 11:00 – 11:30 | <b>Discussion on MVET Model</b>  | Facilitator  |
| 11:30-11:45   | Break  |  |
| 11:45 – 12:45 | <b>Case Study:</b> Reweighting RCT evidence to better reflect real life – a case study of the Innovation in Medicine initiative (IMI - GetReal)<br><b>Discussion of case study implications for retrospective evidence</b>           | Michael Happich – GetReal & Eli Lilly<br>Facilitator                                   |
| 12:45-13:30   | <b>Prospective Discussion: 'Evidence for unmet needs'</b><br>Case study implications for informing multi-stakeholder definitions of unmet medical needs  | Facilitator  |
| 13:30-14:30   | Lunch  |  |
| 14:30-15:00   | <b>Prospective Discussion: 'RWE to inform evidence development plans'</b> Case study implications for using RWE to aid in designing prospective studies  | Facilitator  |
| 15:00-15:30   | <b>Discussion: What actions are needed to enhance or develop RWE repositories fit for purpose for informing the prospective uses?</b>  | Facilitator  |
| 15:30-16:00   | <b>Summary and Next Step Planning</b> <ul style="list-style-type: none"> <li>Leadership summary and proposed next steps</li> </ul>   | H.G. Eichler<br>S. Garner<br>G. Hirsch   |

### Day 2: Could MAPPs with RWE Enhance Evidence, Access and Safety?; Insights from a Gilenya Retrospective Case Study

Facilitated by Dr. Ken Oye – MIT

|               |   |  |
|---------------|---|--|
| 9:30 – 10:00  | Networking & Coffee   |  |
| 10:00 – 10:15 | <b>Introduction to the Day's Process</b>  | K. Oye   |
| 10:15 - 11:15 | <b>MAPPs can enhance patient access for uniformly efficacious therapy</b> <ul style="list-style-type: none"> <li>Concept description and first scenarios</li> <li>Discussion of key findings</li> </ul>   | M. Trusheim, Aiden Flynn - Exploristics<br>Facilitator |
| 11:15-12:15   | <b>MAPPs with RWE can increase patient safety</b> <ul style="list-style-type: none"> <li>The power and challenges of detecting AEs with MAPPs/RWE</li> <li>Discussions on current opportunities and future RWE improvements that could improve detection power</li> </ul> | A. Flynn, M. Trusheim<br>Facilitator                   |
| 12:15 – 13:15 | Lunch   |  |

|               |   |  |
|---------------|---|--|
| 13:15 – 14:15 | <b>Beyond RWE Registries: Pragmatic Trial Opportunities Pre-Authorization</b> <ul style="list-style-type: none"> <li>• Pragmatic Trial Objectives, structure and potential</li> <li>• Discussion on benefits and limitations</li> </ul>                           | M. Trusheim, A. Flynn<br>Facilitator                                   |
| 14:15 – 14:45 | <b>Integrating RWE into MAPPs Lifespan Evidence Development Plans:</b> <ul style="list-style-type: none"> <li>• Discussion of Gilenya Case Study Implications</li> </ul>  | M. Trusheim<br><br>Facilitator   |
| 14:45 – 15:00 | Break   |  |
| 15:00 – 15:30 | <b>Building Evidence Driven Simulation Capabilities to Inform MAPPs and RWE Designs:</b> <ul style="list-style-type: none"> <li>• Overview of connected tools used for Gilenya Case Study</li> <li>• Discussion of future opportunities and directions</li> </ul> | A. Flynn, M. Trusheim,<br>Joost de Folter - <i>NICE</i><br>Facilitator |
| 15:30-16:00   | <b>Summary and Next Step Planning</b> <ul style="list-style-type: none"> <li>• Leadership summary and proposed next steps</li> <li>• Group Discussion</li> </ul>  | H.G. Eichler<br>S. Garner<br>G. Hirsch                                 |

## Annex II: Participant List

**Stella Blackburn**

Vice President  
Global Head of Risk Management  
Quintiles

**Mathieu Boudes**

Operations and Projects Manager  
EURORDIS

**Jacoline Bouvy**

Scientific Adviser  
National Institute for Health and Care Excellence

**André Broekmans**

Director  
Escher  
Lygature

**Anna Bucsics**

Lecturer  
University of Vienna

**Francesca Cerreta**

Senior Scientific Officer  
European Medicines Agency

**Chris Chinn**

Head  
Real World Investigations  
Sanofi

**Elizabeth J. Cobbs**

Executive Director  
Medical Policy & Quality Research  
Merck & Co., Inc.

**Joost de Folter**

Operational Researcher  
National Institute for Health and Clinical Excellence

**Felipe Dolz**

Head  
Global Regulatory Policy & Intelligence  
Sanofi

**Anne-Virginie Eggimann**

Vice President  
Regulatory Science  
bluebird bio, Inc.

**Hans-Georg Eichler**

Senior Medical Officer  
European Medicines Agency

**Stuart Faulkner**

Operations and Programme Manager  
CASMI

**Stephan Fawbert**

Senior Policy Advisor  
Policy Division  
Medicines and Healthcare products Regulatory  
Agency

**Aiden Flynn**

Managing Director  
Exploristics

**Sarah Garner**

Associate Director  
Research & Development  
National Institute for Health and Care Excellence

**Wim Goettsch**

Project Leader  
EUnetHTA JA2 WP5 Rapid Assessment  
National Health Care Institute, The Netherlands

**Alicia Granados**

Head  
Global HTA Scientific Strategy  
Gezyme

**Shahid Hanif**

Head  
Health Data & Outcomes  
The Association of the British Pharmaceutical Industry

**Michael Happich**

Director  
BioMeds HTA - Australia, Canada & Europe  
Eli Lilly and Company

**Adam Heathfield**

Senior Director  
Global Health and Value Innovation Center  
Pfizer

**Gigi Hirsch**

Executive Director, Center for Biomedical Innovation  
& Program Director, NEWDIGS  
Massachusetts Institute of Technology

**Elaine Irving**

Clinical Outcomes Research Director  
GlaxoSmithKline Pharmaceuticals

**Pall Jonsson**

Senior Scientific Adviser  
Research & Development  
National Institute for Health and Care Excellence

**Angelika Joos**

Executive Director  
Regulatory Affairs  
Merck & Co., Inc.

**Alexandre Joyeux**

Head  
Global Patient Access  
Novartis

**Shahin Kausir**

Senior Scientific Assessor  
Vigilance Division  
Medicines and Healthcare products Regulatory Agency

**Finn Børlum Kristensen**

Secretariat Director  
EUnetHTA

**Robyn Lim**

Senior Science Advisor  
Office of Legislative and Regulatory Modernization  
Health Canada

**Murray (Mac) Lumpkin**

Deputy Director, Regulatory Affairs  
Lead for Global Regulatory Systems Initiatives  
Gates Foundation

**Luk Maes**

Executive Director  
Regulatory Policies Europe  
Bristol-Myers Squibb

**Thomas Marshall**

R&D Software Developer  
Exploristics

**David Martin**

Safe Use Initiative Lead  
Professional Affairs & Stakeholder Engagement staff  
FDA Center for Drug Evaluation & Research

**François Meyer**

Advisor to the President &  
Director of International Affairs  
French National Authority for Health (HAS)

**Kenneth A. Oye**

Associate Professor of Political Science &  
Co-Director, MIT Program on Emerging Technologies  
Massachusetts Institute of Technology

**Vinciane Pirard**

Senior Director, Public Affairs  
Genzyme

**Brian Rittenhouse**

Data Program Lead, NEWDIGS &  
Associate Professor, School of Pharmacy  
Massachusetts College of Pharmacy & Health

**Paul Robinson**

Executive Director  
Scientific Medical & Patient Perspective  
MSD

**Andrew Roddam**

Vice President & Head  
Real World Evidence, Clinical Platforms & Sciences  
GlaxoSmithKline Pharmaceuticals

**Solange Rohou**

Senior Director Regulatory Affairs & Policy, EU  
Global Regulatory Affairs, Patient Safety & QA  
AstraZeneca

**Ine Skottheim Rusten**

Scientific Officer  
Norwegian Medicines Agency (NOMA)

**Anja Schiel**

Senior Adviser/Statistician, HTA & Reimbursement Unit  
Department for Pharmaco-economics  
Norwegian Medicines Agency (NOMA)

**Sebastian Schneeweiss**

MIT NEWDIGS Data Program &  
Professor of Medicine and Epidemiology  
Harvard Medical School

**Ad Schuurman**

Head  
Business Contact Centre & International Affairs  
National Health Care Institute, The Netherlands

**Valentina Strammiello**

Programme Officer  
European Patients Forum

**Giovanni Tafuri**

National Expert  
European Medicines Agency

**Christoph Thalheim**

Director  
External Affairs  
European MS Platform (EMSP)

**Adrian Towse**

Director  
Office of Health Economics (OHE)

**Mark Trusheim**

Director, NEWDIGS Strategic Initiatives &  
Visiting Scientist, Sloan School of Management  
Massachusetts Institute of Technology

**Spiros Vamvakas**

Deputy Head  
Product Development Scientific Support  
European Medicines Agency

**Richard West**

Behçets Syndrome Society, UK  
EURORDIS

**Entela Xoxi**

Co-ordinator of AIFA Registries  
Pharmaceutical Policies & Strategies Area  
Italian Medicines Agency – AIFA

**Deborah Young**




Director of Operations, NEWDIGS  
Center for Biomedical Innovation  
Massachusetts Institute of Technology

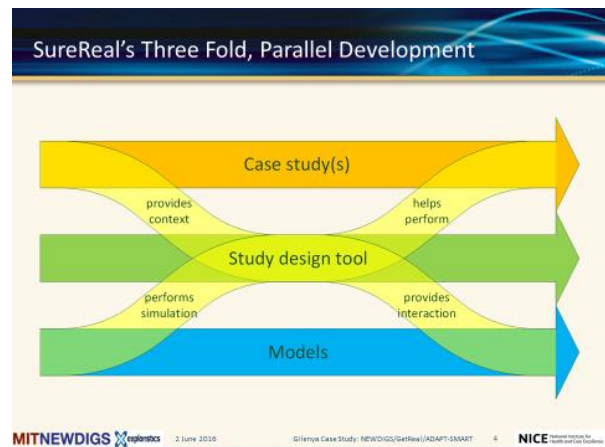
## Annex III: SureReal Capabilities to inform AP and RWE designs

Higher resolution images were distributed in an accompanying document

### SureReal Main Objectives

- Provide insight on the use of real world evidence and MAPPs in clinical drug development through analysing case studies, beginning with today's
- Develop an interactive simulation modelling tool to assess the impact of implementing alternative evidence generation strategies on patient access, payer cost and innovator incentives




MITNEWDIGS  2 June 2016  NICE  NICE

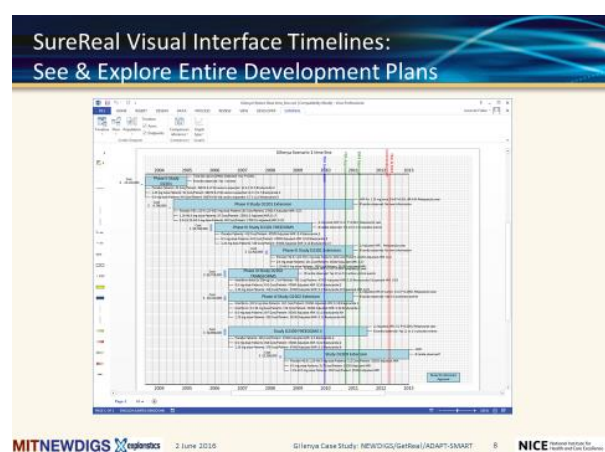
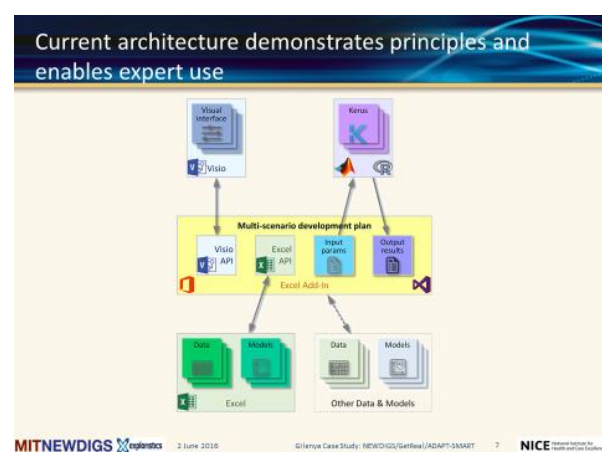
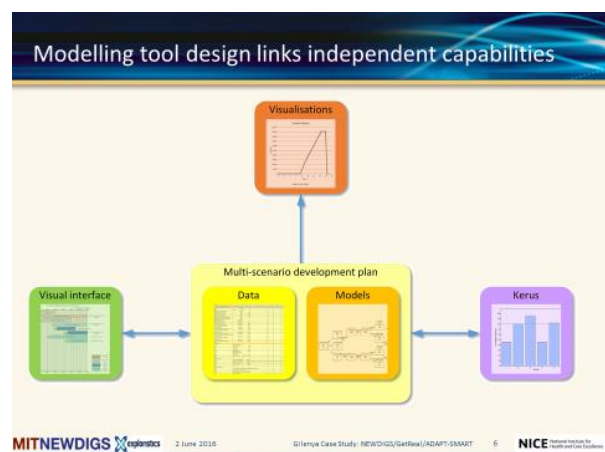


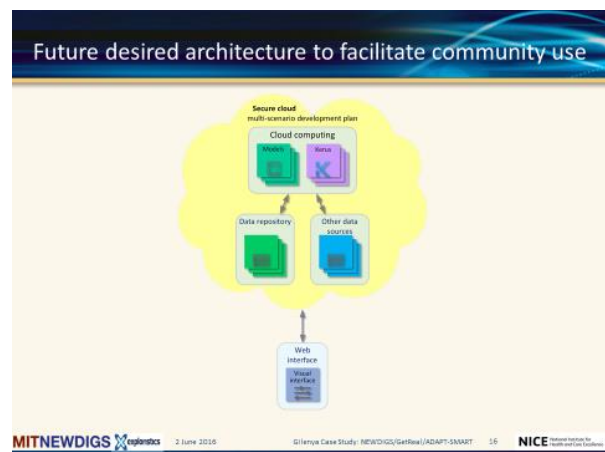
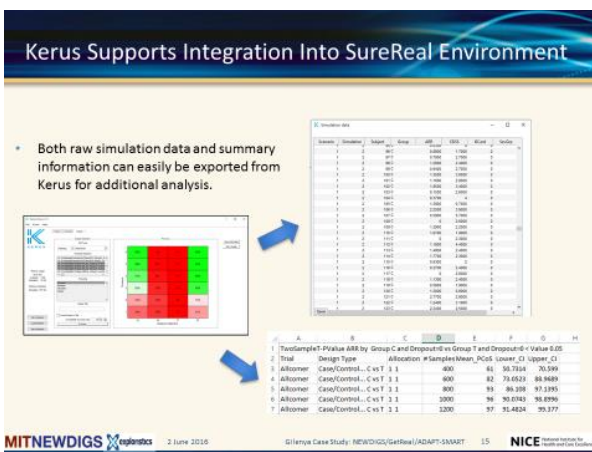
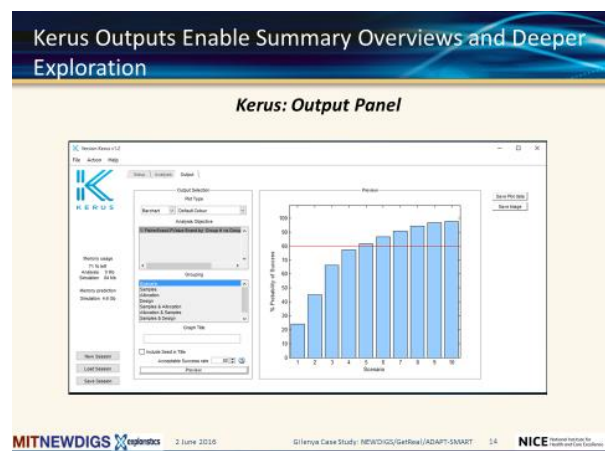
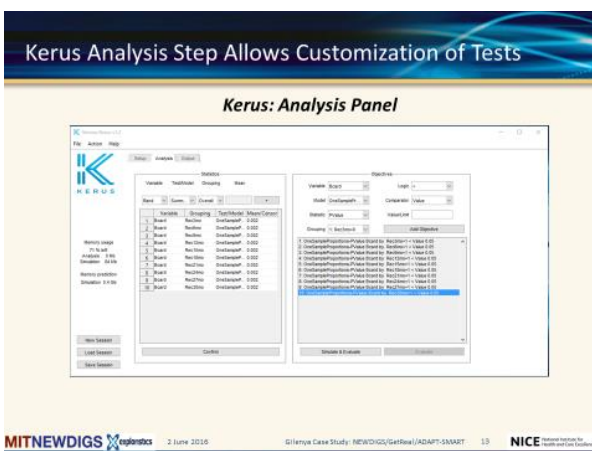
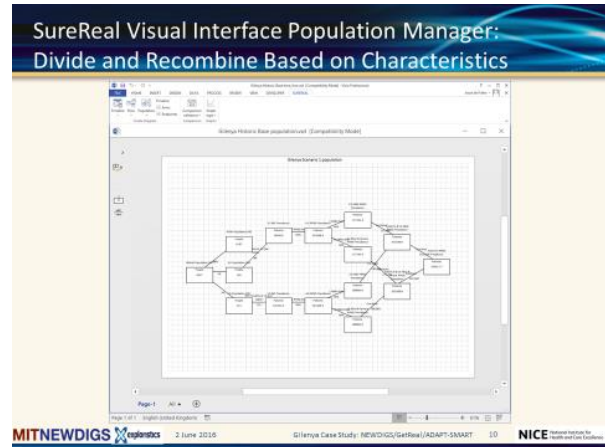
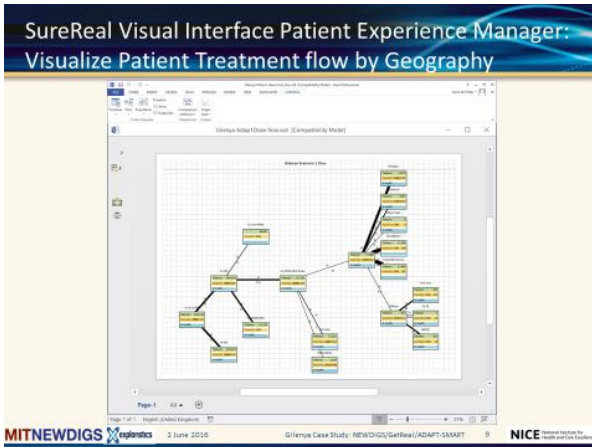
### Follows Janus Technical Architecture Principles

- **Integration** of best of breed models as well as development of new ones
- **Transparency** of inputs, algorithms and results
- **Open Access** of environment and tools to the community
- **Alternative scenario management** and comparison
- **Collaboration** in creating a software and organizational environment to facilitate the above

Trushchen, Boris, Garret, Lin, Patel, Hirsch. This is an initiative to multi-stakeholder process and tool set for facilitating and quantifying Adaptive Licensing discussions. Health Policy and Technology 3:341-347 (2014). <http://dx.doi.org/10.1016/j.hpt.2014.10.004>

MITNEWDIGS  2 June 2016  NICE  NICE





Joost de Folter (*GetReal/NICE*) was the primary contributor to the SureReal environment development. Exploristix provided its Kerus modeling software & analysis support pro bono.

IMI Disclaimer: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.