MISG New Technologies Forum on Umbrella/Basket Protocols

A joint meeting of the ABPI and MHRA
Royal College of General Practitioners, London
27 October 2015

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Foreword

The ABPI and MHRA established the Ministerial Industry Strategy Group (MISG) New Technologies Forum in 2007 to provide a platform to horizon scan scientific developments with potential high impact on the regulation of medicines. The meetings aimed to raise awareness and understanding of the topics to advance medicines development, producing future recommendations to support further progress in these areas. Topics explored at previous meetings include regenerative medicine, clinical trial design, early access, biomarkers, personalised medicines and physiologically-based pharmacokinetic (PBPK) modelling and simulation.

The Forum meeting on 27th October 2015 was convened to explore the challenges that surround the use of Umbrella/Basket protocols. Umbrella and basket protocols play a key role in the development of stratified medicines, but the delivery and regulatory use of these complex trials raises a number of challenges. This meeting examined current and prospective industry and academic use of umbrella and basket protocols alongside perspectives from key regulatory agencies.

Following a productive meeting including global industry, global regulators and academics, we are very pleased to publish this Forum meeting report and it has enabled us to identify substantial areas to follow-up. This Forum, and future meetings and discussions, will support and enhance the use of these trial methodologies as a tool for the development of stratified medicines for patient benefit.

Mike Thompson
ABPI Chief Executive

Ian Hudson
MHRA Chief Executive

Executive summary

Precision medicine is based on matching the mechanism by which a therapeutic (or drug) works to a patient population selected for treatment based on a marker (or markers) that identify the "targeted" biological mechanism that underlies the disease state; the close alignment of disease driver and drug mechanism should achieve greater disease control, and so improved clinical benefit. With increasingly greater disease definition, driven by increasingly complex characterization at the molecular level, there is an inevitable increase in disease subtypes that define smaller, but better characterized, patient populations. It should be considered whether the more traditional, long-established processes for drug development and market approval are perhaps less adapted to this increasing complexity. There is benefit to further discussion and description of the processes, methods and governance routes required to successfully support the development and market approval of precision medicine products. Oncology has been at the vanguard of precision medicine and has helped identify core challenges and areas for consideration.

Technological advances continue to address better disease definition, and modern drug development techniques provide increasing novel therapeutic options, so the key challenges lie in the operational aspects of clinical studies to evaluate new targeted therapeutics. Clinical trial designs such as umbrella and basket studies have emerged as potential solutions to these hurdles, but in themselves have significant challenges for implementation. Similarly, the data sets from such studies (and precision medicine approaches in general) have stimulated adaptation in the established processes used to evaluate the clinical evidence base supporting new drug approvals. Meanwhile conditional licensing and early access mechanisms are enabling early patient access to new medicines.

Against this rapidly changing landscape, it is timely to ask if existing processes and mechanisms are best placed to support the development of precision medicine products.

The Workshop: The Ministerial Industry Strategy Group (MISG) New Technologies Forum on Umbrella/Basket Protocols brought together stakeholders from industry, academia, regulatory

authorities, clinical practice and patient groups to review the needs of precision medicine product development, with a specific focus on 1) the mechanisms to develop an appropriate clinical evidence base, and 2) the mechanisms and dialogue employable during the regulatory process towards market approval.

Emerging Themes: discussions highlighted a range of challenges:

- ***Research-clinical integration***: whilst routine clinical practice provides a fertile environment for research and an ideal base to generate key understanding, it remains challenging to embed research and research practices. Development of mechanisms to enable this integration could yield significant benefits.
- ***Cooperative platforms for recruitment***: operational solutions to the challenges of running clinical trials in increasingly smaller subpopulations of marker-defined patients include umbrella and basket trials. These are significantly enabled through the development of large-scale regional, national and international screening initiatives, tumour-based consortia and public-private initiatives. Further development, implementation and use of collaboration and/or cooperative mechanisms will be central to future clinical trial conduct and the development of clinical evidence.
- ***Academic data sets***: data gained in academic studies, typically in the earlier phases of drug development, offer valuable clinical evidence and there will be an increasing desire to utilize such data in addition to that from industry-sponsored trials to support regulatory interactions. The nature of data gained in academic studies varies, so guidance is needed on its suitability for such purposes, and required minimal quality/content.
- ***Composite data sets***: the clinical evidence base supporting a precision medicine product will increasingly be derived by accumulating data from a number of smaller-scale, independent clinical studies. The ability to integrate such data for regulatory consideration will be facilitated by guidance on the needs for greater consistency across trials (for example, in terms of definitions, endpoints, dosing, screening methodologies and consent procedures)
- ***Control data***: the potential for notable clinical benefit from precision medicines places pressure on the feasibility of conducting randomized trials, driving an increasing use of single-arm (targeted agent only) studies and a desire to use these data for regulatory purposes. There is a growing need to understand the potential to generate and use comparator (control) data from other sources (for example, historical or observational epidemiological data).

- ***Dialogue and available mechanisms***: open dialogue between parties such as industry and regulators will provide the best opportunity for successful outcomes; to support this, it may be useful to ensure awareness of existing mechanisms for, and types of, regulatory interaction (informal and formal), and outline new opportunities aligned to any specific needs of precision medicine. If existing mechanisms are only used to a limited extent, it would be useful to explore why and provide solutions.

Proposals for next steps: several opportunities were identified that would allow early success, and should be considered for next steps.

- ***Integrating data sets***: there are increasing opportunities to integrate data sets generated across a variety of related studies performed in different environments (for example, academic, industry-sponsored) to form a body of clinical evidence to support regulatory interactions and licensing applications. Guidance on minimal requirements for standards, accommodating increasing protocol flexibility, understanding new outputs from new methodologies and how such data can be integrated, would be facilitating.
- ***Using existing data***: there is considerable scope to leverage existing data for comparator/control data sets, particularly to support the increasing use of single-arm studies. Guidance on suitability, methods and opportunities, as well as supporting innovation in statistics and trial analysis methodologies (and related) would be enabling.
- ***Communicating opportunities for dialogue***: current awareness and use of existing mechanisms for dialogue and guidance with regulators (informal, formal, parallel) may not be maximal; improving awareness, education and engagement would be greatly beneficial.
- ***Multistakeholder dialogue***: dialogue with regulators may benefit from wider representation, for example including representatives and investigators from cooperative industry-academic collaborations in addition to industry. Development of mechanisms to enable broader expert representation and input would enrich discussions and understanding.

Introduction

(adapted from; Hollingsworth & Biankin, Public Health Genomics. 2015;18(6):338-348)

We are seeing a rapid expansion in precision medicine founded on the potential for durable clinical benefit and driven by rapid and substantial developments in the understanding of the molecular basis of disease coupled with the in-parallel development of new therapeutics, and diagnostic modalities designed to (more) specifically target and treat mechanisms thought to drive the disease process. It is a simple central tenet – match a drug and its mechanism of action to patients identified with a selection marker(s) predictive of response, and you should achieve more durable clinical benefit. The potential benefits are clear for all stakeholders: at the centre are patients (and physicians) for whom more options, durable clinical benefit, reduced exposure to non-effective drugs and the potential to leverage current scientific and technological advances are compelling arguments; for the pharmaceutical industry, the potential to tackle core challenges in discovering and developing more effective medicines, reduce rates of attrition in drug development, and reduce the associated escalating costs which are central to a more sustainable future and delivery for healthcare needs; for healthcare systems and payers, improved efficiency through the provision of efficacious and cost-effective care through the avoidance of ineffective and redundant interventions, are again key to a more sustainable and deliverable future system. Current established drug development processes and pathways for regulatory approval originate from a pre-precision medicine time, being based on a more conventional sequence of Phase I, Phase 2 and Phase 3 clinical trials used to generate the body of clinical evidence needed to support application for market approval. The needs of precision medicine development, however, are not met by this approach.

Increasing resolution of disease definition results in increasingly smaller populations of patients being defined by a marker or markers used to select for treatment. The direct consequence is having fewer patients eligible for clinical trial enrollment, raising significant challenges to the ability to conduct the type and scale of more traditional clinical trials. Development of large-scale regional, national and international screening initiatives, tumour-based consortia and public-private initiatives have emerged as mechanisms to help identify sufficient numbers of patients within more tightly defined subpopulations. In addition, clinical trial designs such as ‘umbrellas’ and ‘baskets’ (see Glossary below) have emerged as potential solutions to tackle the operational challenges of clinical testing. Where previously fewer larger-scale and uniform

studies may have been conducted through industry sponsorship, increasingly smaller studies and from varying environments (industry, academic) are producing the data needed to support application for regulatory approval. In turn, and driven in part by the notable clinical benefits being seen, mechanisms such as conditional licensing and accelerated access have emerged as regulatory solutions to help accommodate this change in type and use of clinical evidence.

However, challenges in developing precision medicines are increasingly clear, and are in turn driving adaption and innovation in all aspects from the basics of clinical trial design through to use of statistical methods and the mechanisms used within the healthcare system to develop, approve, adopt and use precision medicine products. Whilst there are potential solutions being developed to the more operational challenges faced in clinical trial conduct and delivery, there is collectively less experience to date with the types of data sets generated and how these might be used as the clinical evidence base used to support market approval. Key outstanding questions include, but are not limited to:

- How might data sets generated from diverse and (potentially) less homogeneous clinical trials be integrated into a single body of evidence?
- What are the minimal requirements and standards needed to enable diverse data set integration? Are there supportive clinical trial design features that could be more commonly incorporated?
- How can existing sources of data be used to support the required evidence base; for example, for comparator/control purposes?
- Do existing mechanisms for seeking advice and guidance from regulators on the suitability of such approaches and data sets support the changing and emerging needs?
- How can effective regulatory decisions be made on smaller, more diverse data sets and initially less complete evidence than traditionally used?

Precision medicine has the potential to profoundly change how new drugs are developed. How healthcare systems, regulators and other stakeholders adapt to these changes and ensure patient access to safe and effective medicines in a timely manner remains critical. The MISG New Technologies Forum on Umbrella/Basket Protocols brought together stakeholders from industry, academia, regulatory authorities, clinical practice and patient groups using recent real world examples and experience to consider specific steps to enable and guide the development and use of data from basket and umbrella clinical trials for regulatory approval.

Glossary: based on cancer drug development

Umbrella trial – a single trial that allows testing of multiple targeted agents across different trial arms against molecularly characterized cancers of a single type, e.g. non-small cell lung cancer

Basket trial – follows the same principle as an umbrella trial, but includes cancers of multiple histological type

Presentations

Regulatory context

Rob Hemmings (MHRA) described the MHRA's current framework for managing precision medicine products, which sits within a wider European regulatory context. The legal framework for decision-making in respect of marketing authorisations is relatively flexible, focusing on the need to demonstrate therapeutic efficacy and to consider risk-benefit balance but without specifying how this should be done. Hence there are no formal legal obstacles to the use of novel forms of evidence in the form of data sources or trial designs.

Marketing authorisation can be granted following evaluation of a comprehensive clinical dossier; the authorisation may or may not be associated with measures for post-authorisation data collection. Conditional marketing authorisation may be granted if there is an immediate unmet medical need to be addressed such that the potential benefit outweighs uncertainties inherent in the clinical evidence base being incomplete; further post-authorisation data collection is subsequently required. The MHRA also recognises that, in some situations, it may not be possible to develop a comprehensive clinical dossier, and Marketing Authorisation under Exceptional Circumstances provides a tool for dealing with such situations.

The scientific committees (e.g. CHMP) of the European Medicines Agency (EMA) have released a series of guidelines in areas such as pharmacogenomics, cancer drug development, study of small populations and companion diagnostics. Both MHRA and EMA also provide scientific advice to companies, open to discussions at any stage of drug development, for example on the type of evidence that is likely to be required to support an application for marketing authorisation of a targeted therapy. It is also possible to obtain parallel advice from the EMA and Food and Drug Administration (FDA), from the EMA and Health Technology Assessment (HTA) bodies, and from

MHRA and National Institute of Clinical Excellence (NICE), although these mechanisms, in particular the opportunity to obtain global regulatory advice with FDA, are currently little used.

Specific mechanisms exist for orphan products, to incentivise drug development for low-prevalence conditions. These mechanisms can be applied to medicines for patient subgroups defined by specific biomarkers, as long as the biomarkers are not arbitrarily chosen but relate to the specific mechanism of action of the drug and define a clinically distinct target population.

The MHRA has now had experience of licensing several targeted therapeutics, and considered evidence from both controlled and uncontrolled trials. It offers advice on the appropriate design of umbrella and basket trials and recognises the need to adapt to challenges posed by precision medicine and for flexibility and dialogue, including discussion of practical challenges as well as scientific evidence requirements.

Industry perspective

To outline some of the challenges of drug development for low-prevalence patient groups, **Andrew Mortlock** (AstraZeneca) described the development of AZD4547, a fibroblast growth factor receptor (FGFR) inhibitor.

The *FGFR* gene is amplified in 5-7% of gastric cancers. Encouraging pre-clinical data on AZD4547 supported progression to a clinical trial, for relapsed gastric cancer characterised by *FGFR2* polysomy or amplification (the SHINE study). However, even with multiple international centres, recruitment proved extremely difficult, with attrition throughout the screening procedure. Some highlighted challenges included quality assurance of testing within one centre over the duration of the study, and the duration of time to complete screening and return results in the context of a rapidly progressive disease. Ultimately, more than 70 patients were pre-screened for each patient dosed.

Further complexity arose from the discovery that *FGFR* copy number was lower than expected in SHINE patients, but had a significant impact on response to AZD4547. This raises the question of the appropriate threshold to guide use of the drug in patients. As well as inter-patient heterogeneity, variation was also seen within patients – relapse was seen in a patient whose tumour included cells in which *FGFR* was not amplified.

Compared with other kinase inhibitors, the AZD4547 and gastric cancer combination had several features that made drug development and recruitment particularly difficult. One advantage, however, is that *FGFR* mutations are seen in multiple other cancers, so AZD4547 might have potential uses outside gastric cancer. More generally, the case highlights the huge challenges in recruitment for low-prevalence conditions, particularly for aggressive disease where patients have severely limited life expectancy.

Another pathfinder for precision medicine in oncology is crizotinib, described by Dr **Richard E Buller** (Pfizer). Crizotinib is a small-molecule tyrosine kinase inhibitor active on several targets (c-MET, ALK and ROS1). Beginning in 2006, it was assessed in a quintessential precision medicine trial, the A8081001 study. This was both an umbrella study, examining a range of molecular abnormalities in lung cancer, but also a basket study, including samples from other cancer types with c-MET, ALK or ROS abnormalities. Notably, the trial design has been highly adaptive, undergoing 22 amendments to date, requiring regular dialogue with regulators.

The drug received accelerated FDA approval in August 2011, full approval for recurrent ALK-positive disease in November 2013, and approval for broad ALK-positive use in September 2015. EMA conditional approval was granted in October 2012 for previously treated ALK-positive non-small cell lung cancer (NSCLC). In April 2015, it was awarded FDA Breakthrough Therapy designation for ROS1-positive NSCLC.

Although data from the single-arm A8081001 trial formed the basis for an initial FDA submission, accelerated approval relied on data from a single arm expanded access trial, A8081005*, in part because of complexities linked to the use of a companion diagnostic. A8081001 trial data then served as supportive data.

Crizotinib illustrates further complexity in precision therapy evaluation. It acts on multiple targets and may be suitable for multiple diseases; furthermore, its molecular targets may be affected by multiple mutational processes. The paradigm of 'one target/one drug/one test' delivering clinical benefit no longer applies.

* Erratum: When the report was originally issued trial A8081005 was identified as a randomized follow-up trial. It was in fact a single arm expanded access trial.

The new approach raises other important issues. For example, how many patients need to be studied? How effective is the biomarker selection strategy? How can effects on biomarker-negative patients be identified? Could a biomarker used to select responsive patients actually be a prognostic rather than predictive factor? A therapy may look effective simply because it has been tested on a subset of patients with an innate survival advantage. Analysis of epidemiological data from molecularly profiled patients may help to address questions of preferential survival, and further insight into efficacy can come from inter-patient and intra-patient analysis of trial data.

Additional challenges for regulators include the difficulties of identifying rare adverse events in small trials (emphasising the need for post-authorisation surveillance studies) and the appropriate mechanisms for supplemental uses of licensed medicines. Lower thresholds may be appropriate for supplemental uses when a solid body of data already exists on an agent.

Academic perspective

As the above examples illustrate, approaches that start with a single therapeutic agent typically face huge recruitment challenges. A more efficient alternative is to adopt a more patient-centric approach, characterising patients' cancers and then identifying suitable clinical trials. **Nicholas Turner** (Institute of Cancer Research) described how this approach can work in practice.

Diseases such as breast cancer are characterised by huge genetic heterogeneity, with some commonly mutated genes but also huge numbers of rare (but potentially targetable) genetic changes. Whole genome sequencing of metastatic biopsies can be used to identify such genetic changes, enabling patients to be routed to the appropriate clinical trial, as exemplified by the SAFIR02 trial in France and AURORA programme run across Europe by the Breast International Group.

Professor Turner described an alternative approach based on the analysis of circulating tumour DNA to identify actionable mutations. The UK Plasma MATCH study is testing this approach with 40-50 screening centres and 20 treatment centres, with centralised testing at the Royal Marsden Hospital. This kind of high-throughput platform-based strategy, using readily accessible samples, could be a powerful way to address the logistical challenge of recruitment. To recruit

200 patients with a mutation affecting 3% of patients for a phase III study, some 11,000 patients would need to be screened (16,000 for a mutation affecting 2% of patients).

Nevertheless, the degree to which such studies can provide data suitable for regulatory approval is open to debate. Molecular screening is being delivered to ISO standards, but the trial is being run by an academic clinical trials group and data will be owned by an academic institution. Data are being collected robustly but not in a fashion that would support traditional filing.

Professor Andrew Biankin (University of Glasgow) highlighted some of the considerable cultural and practical challenges to precision medicine. Having contributed to the International Cancer Genome Consortium, Professor Biankin sought to use the wealth of data in pancreatic cancer to test more personalised treatment approaches. The IMPaCT (Individualised Molecular Pancreatic Cancer Therapy) trial randomised patients to standard or personalised therapy, the latter involving use of four tailored regimes depending on the presence of low-prevalence mutations.

Although the trial proved feasible, it highlighted many of the practical challenges to the introduction of precision medicine. In particular, health systems are currently not geared up to integrate experimental approaches, and many physicians have yet to appreciate its likely impact.

Furthermore, Professor Biankin argued that the conventional model of evidence-based medicine is no longer viable in precision medicine. Generating evidence through traditional large trials is simply impractical: individually recruiting patients for trials in low-prevalence conditions means discarding large numbers of patients and incurs huge screening costs. Furthermore, while evidence might be generated for a specific mutated gene, there is no guarantee that different mutations in that gene have the same functional effects.

Professor Biankin therefore suggested a more pragmatic approach is required, with drug development paradigms reshaped to reflect the challenges of low-prevalence mutations and the need for associated biomarkers. Central to this new model is the adoption of more patient-centric approaches, in which more routine cancer profiling allows patients and clinicians to select the most appropriate current trial. The PRECISION-Panc initiative is attempting to apply this model, integrating discovery research and pre-clinical studies alongside a master protocol-based umbrella trial.

Introducing discussions, Professoir Sir **Munir Pirmohamed** (University of Liverpool) emphasised that cancer was acting as a pathfinder that other disciplines would follow as molecular understanding of diseases improved. While 'hierarchies of evidence' typically privilege randomised controlled trial data, there are a diversity of ways in which useful evidence can be generated to inform decision-making. He suggested we are in an era of considerable innovation, in trial design and in the growing use of real world data and moves towards learning health systems. Marketing authorisation may increasingly come to be seen as one step in an ongoing process in which decisions are modified in light of accumulating evidence on effectiveness, safety and cost-effectiveness. He also emphasised the importance of involving the public and patients in decision-making.

Similarly, Professor **Martin Gore** (Royal Marsden Hospital) argued strongly that attention should be given to clinical context. Trial design needs to consider not just 'pure' issues of evidence quality but also 'applied' matters, such as fairness to patients – particularly the possibility that randomisation could deny patients potentially effective treatments. He highlighted the importance of cross-over designs to minimise this possibility. He also emphasised the importance of learning from routine clinical use, and for enhanced access to clinical data, particularly clinical trial data (from industry and academia) to support regulatory decision-making. Optimal, and perhaps novel, statistical methodology may be developed to address challenges in clinical trial methodology arising from the fact that many more people will be classified as having a 'rare' tumour. Caution was also raised that with the dynamic nature of tumour heterogeneity, precision for an individual patient was something of a moving target.

Discussions

A large part of the meeting was given over to discussion in break-out groups around the following two topics.

Breakout Session 1

Increasing disease (hyper-)segmentation and required magnitude/duration of clinical effect are driving precision medicine approaches to be embedded at the earliest stages of drug development, but the need to identify and study low(er) incident patient populations challenges conventional development and approval pathways. Basket/umbrella trials are facilitating clinical

investigation; however, the evidence base for clinical efficacy in selected patient populations will ever more involve data from multiple studies and varying sources (industry-sponsored, academic, etc.). Ensuring the data generated by these studies, and its integration from multiple sources in to a single dossier acceptable for market approval is critical;

i. What are the limitations of the current environment to conduct such clinical trial approaches, and the trial designs being utilized?

ii. What are the needs of the stakeholder groups – pharmaceutical industry, small-medium sized enterprises, regulators, physicians, patients, payers?

iii. Can we remove some of the perceived barriers for delivery?

iv. Where can guidance be agreed to tackle the real hurdles identified?

Breakout Session 2

The current pathway of regulatory interaction was designed to support conventional drug development approaches and other pathways may be required to fully support precision medicine;

i. What are the limitations of the current guidance, the pathway and environment for regulatory interactions?

ii. What are the needs of the stakeholder groups – pharmaceutical industry, small-medium sized enterprises, regulators?

iii. Can we remove some of the perceived barriers for delivery/better interaction?

iv. Where can guidance be agreed to provide a more productive/conducive pathway for regulatory interaction?

Some of the themes discussed and questions raised are documented below.

Platforms and collaborations

Whilst not the primary focus for the industry-regulator interaction, the group proposed some areas for collaboration between industry, academia and the UK healthcare system to facilitate patient recruitment and integration of data between different sources.

More effective embedding of research in clinical care would be highly beneficial, not least in avoiding the duplication of infrastructure.

In terms of recruitment, with stratified patient groups and low-prevalence variants, identifying patients suitable for studies presents an ever-greater challenge and this has a dramatic effect on screening costs and overall study costs. To best facilitate recruitment, patients would be routinely characterized (usually genotyped), supporting enrollment in appropriate clinical trials. The use of umbrella protocols matching the mechanism by which a therapeutic works to a patient population selected for treatment based on a marker (or markers) are likely to be efficient. Cooperative platforms are likely to be well placed to deliver continuous clinical trials, which may bring efficiencies over the 'stop-start' approach of multiple independent trials each with a separate sponsor, and may be particularly relevant to the exploratory phase of drug development.

Inconsistencies in assay methodology between different pathology laboratories and independent assay development by multiple companies renders the challenge of reliably integrating data from different sources difficult or even impossible; more work in this area might be brought into pre-competitive space to promote consistency. More broadly, data capture in clinical practice and research can differ, which risks compromising opportunities to learn from data in clinical practice. New ways are needed to incentivise clinicians so that research-quality information is captured more routinely. Consistent data capture and recording standards across data sources (clinical practice, registries, clinical trials) will clearly facilitate integration of data and may permit strategies such as availability and utility of external control arms for prospective clinical trials. These benefits may be best leveraged through construction and maintenance of overarching databases per disease state.

Trial design and innovation

Whilst it may be impractical to attain the trial sizes that are conventional for Phase III randomized controlled trials, this might not be necessary if the signal:noise ratio is greater having properly targeted the intervention. A randomized controlled trial remains the most robust source of data to support marketing authorization but if the evidence from pre-clinical and exploratory work is strong, the need for, and the ethics of, randomization will need to be discussed. Approval based on single-arm clinical trial data is not precluded if the evidence for efficacy is compelling. Within-patient comparisons can also be useful, in particular where the intervention extends time to disease progression compared to earlier lines of treatment. Notwithstanding, difficulties with creating external control groups on the basis of current epidemiology are recognized. Broader, untargeted, patient cohorts may not provide a reliable basis for comparison if the biomarker used

for patient selection might have prognostic value (in addition to being predictive for drug effects) and external cohorts reflecting the clinical trial population are not routinely available.

Patient recruitment to trials, especially in life-limiting diseases, can be challenging if a placebo arm is included. Crossover designs which allow patients to move onto the therapeutic arm if benefit is demonstrated are becoming more prevalent and are increasingly accepted by the regulators. However, these can also offer challenges with respect to collecting appropriate endpoints that meet the needs for both regulators and HTA bodies.

It is to be expected that knowledge about the biomarker to be used for patient selection accumulates rapidly with clinical trial experience, specifically in respect of assay development and validation and criteria for determining marker positivity. The optimal strategy for integrating accumulating knowledge into a development programme is likely to remain a topic for case-by-case discussion, in terms of designing an efficient clinical trial programme and in terms of conducting sponsor/regulator interactions.

Novel trial designs such as adaptive designs, basket trials and umbrella trials are welcome in principle, and the utility of each for a given development programme should be the subject of sponsor/regulator interaction. Some methodological issues remain, for example the extent of flexibility within an adaptive trial planned to provide confirmatory evidence of efficacy, methodological standards for generating reliable indirect comparisons (to external control groups), the role of basket trials in the confirmatory phase of drug development and whether there exist scenarios in which the analysis and interpretation of these basket trials in oncology can be 'histology-agnostic'. Reticence on the part of any stakeholder to implement novel designs only because of lack of familiarity will need to be addressed. Positive experiences should be shared and scientific objections discussed openly to build common understanding.

Sponsors should take care that trial inclusion / exclusion criteria are fit-for-purpose and do not exclude patient subsets unnecessarily (e.g. through arbitrary age cut-offs, use of other medicines), in particular when aiming to provide confirmatory evidence of efficacy.

Data requirements

Regulators may be willing to accept data from a range of sources as evidence to support a marketing authorisation application, but it is unclear to developers how data from academic-sponsored trials can be used to support filing. Further considerations relate to ownership of data, data standards / compliance with GCP (as appropriate), and reporting standards. Challenges were raised on requiring all data to be compliant with the ICH standards for data collection and reporting of Clinical Study Reports; data requirements are perceived to be onerous; it may be worth examining whether some data are redundant, to streamline procedures.

Enhanced systems for collecting long-term safety data on use of medicines in clinical practice would be beneficial and are of particular importance where a novel medicine is licensed based on a small clinical trial data set.

Interactions with regulators

There is a lack of awareness of the opportunities for dialogue with regulators; a summary of available options for interactions, and associated fees and timelines, would be welcome. This includes options for parallel interactions between regulators in EU and US, and between EU regulators and EU HTA bodies and the opportunities for academic groups to engage directly with regulators. Discussions should then continue on whether additional types of interaction are required in respect of developing a precision medicine. For example, opportunities for dialogue that are sufficiently rapid to inform trial planning or conduct as data emerge, but that are still held on behalf of the entire regulatory network (not only the opinion of those directly involved in discussion). The involvement of EU regulators on a trial data monitoring committee was raised, but this has always been considered incompatible with a regulator's core responsibilities. Wider multi-stakeholder discussions, both general and development programme specific, may be particularly important to understand the economic implications of precision medicine and promote joined-up approaches to address the evidence needs of regulators and other stakeholders (HTA bodies, payers, policy-makers, clinical decision-makers).

Regulators are not bound to randomized controlled trials of conventional size and design to support authorisation, but because regulatory guidance documents are high-level, and detailed

sponsor interactions are held confidentially, it is not always clear how alternative approaches translate to changes in practice; precedent and case studies could be used to communicate how new models for development are being applied.

Parallel pathways and other regulatory processes

The conditional marketing pathway has been available since 2006/7. Early and improved planning of pre- and post-authorisation data collection can lead to a better use of this approval route, subject to agreement from all stakeholders on the levels of evidence to be generated.

There is a perception that the different global regulatory agencies have differing regulatory processes for example, it was suggested that the FDA maintains a lower regulatory bar; although there are examples of medicines approved in Europe but not in the USA.

Opportunities for updated guidelines and additional flexibilities in regulatory processes should be monitored as awareness grows of the particular challenges and opportunities arising in precision medicine. For example, it was remarked that orphan drug designation is applied differently in the EU and USA. Further exploration into whether differences in policy exist routinely could be valuable. As a second example, EU legislation on companion diagnostics differs to that in the US and the scope of the potential for regulatory dialogue on that point could be clarified.

Conclusions and next steps

The meeting concluded with some proposals for subsequent actions, focusing on those aspects of the dialogue that ABPI and MHRA can influence directly. These included generating documentation of opportunities for dialogue with regulators; further discussion on the use of data from disparate sources to construct a marketing authorization application, and the promotion of case studies to highlight good practice and acceptable methodology, identifying opportunities for further research. These ideas will be further developed by the group charged with planning the meeting and will be documented elsewhere.

APPENDIX 1: Delegate list

First Name	Last Name	Organisation
Hesham	Abdullah	MedImmune
Pau	Aceves	Takeda
Liz	Allen	Quintiles
Deborah	Ashby	Imperial College London
Kate	Beaujeux	MedImmune
Nicky	Best	GlaxoSmithKline
Andrew	Biankin	University of Glasgow
Rich	Buller	Pfizer
Janet	Darbyshire	Chair
Erling	Donnelly	Pfizer
Martin	Gore	Royal Marsden Hospital
Russell	Hamilton	Department of Health
Ray	Harris	Eisai
Rob	Hemmings	MHRA
Simon	Hollingsworth	AstraZeneca
Shirley	Hopper	MHRA
Ian	Hudson	MHRA
Robert	Iannone	AstraZeneca
Louise	Jones	MRC
Ian	Jones	Medical Writer
Alexandre	Lambert	BMS
Rebecca	Lumsden	ABPI
Juliet	McColm	Lilley
Peter	Mortimer	AZ/Medical Writer
Andrew	Mortlock	AstraZeneca
Dan	O'Connor	MHRA
Beatrice	Panico	MHRA
Mahesh	Parmar	MRC Clinical Trials Unit
Francesco	Pignatti	EMA
Munir	Pirmohamed	University of Liverpool
Krishna	Prasad	MHRA
Kerry	Rosenfeld	Duchenne Research Fund
Chris	Rowe	InnovateUK
Nina	Selaru	Pfizer
Sunayana	Shah	ABPI
Rowena	Sharpe	Cancer Research UK
Nick	Turner	Institute for Cancer Research

APPENDIX 2: Agenda

Time	Topic	Lead	
09:30 – 10:00	**Coffee and registration**		
10:00 – 10:10	**Introduction**	**Professor Janet Darbyshire (CHAIR)** **Dr Ian Hudson**	
10:10 – 10:15	**Background to meeting**	**Dr Simon Hollingsworth**	
10:15 – 10:30	**Regulatory experience** *MHRA's experience handling and reviewing stratified medicine products*	**Rob Hemmings** **Dr Krishna Prasad**	
10:30 – 11:00	**Industry perspectives** *Industry's experience of umbrella/basket protocols for stratified medicine products* i) Case example 1 (AZD4547): AstraZeneca ii) Case example 2 (crizontanib): Pfizer	**Dr Andrew Mortlock** **Dr Rich Buller**	
11:00 – 11:35	**Academic perspectives** *Experience carrying out umbrella/basket protocols for academic studies in the UK* i) Generating data in low prevalence segments ii) Building and implementing a national precision medicine framework	**Professor Nick Turner** **Professor Andrew Biankin**	
11:35 – 12:00	**Discussants** *Framing the two afternoon break-out sessions*	**Professor Munir Pirmohamed** **Professor Martin Gore**	
12:00 – 13:00	**Lunch**		
13:00 – 14:15	**Break-out session 1: Questions below** *i) Intro and question framing (15mins)* *ii) Discussion (60mins)*	**Group 1** **Lead: Dr Simon Hollingsworth**	**Group 2:** **Lead: Rob Hemmings**
14:15 – 14:40	**Feedback and summary – both groups:** *Break-out session 1*	**Dr Simon Hollingsworth** **Rob Hemmings**	
14:40 – 15:00	**Coffee**		
15:00 – 16:15	**Breakout Session 2: Questions below** *i) Intro and question framing (15mins)* *ii) Discussion (60mins)*	**Group 1** **Lead: Dr Simon Hollingsworth**	**Group 2:** **Lead: Rob Hemmings**

16:15 – 16:40	**Feedback and summary – both groups:** ***Break-out session 2***	**Dr Simon Hollingsworth** **Rob Hemmings**
16:40 – 17:00	**Summary and next steps**	**Professor Janet Darbyshire**
17:00	**Close**	

APPENDIX 3: Pre-read material

The following reference was highlighted as essential pre-read material feeding in to the discussion at the meeting:

Biankin, Piantadosi and Hollingsworth 2015 *Nature* 526:361-370 Patient-centric trials for therapeutic development in precision oncology.