

MRC Stratified Medicine Strategy Workshop Report



Executive Summary

The MRC held a Workshop in June 2013 to inform its Stratified Medicine Strategy. The key recommendations of which are as follows:

Stratified medicine has the potential to improve patient outcomes. To achieve this it is necessary to recognize that diseases are syndromes existing of different pathobiological sub-groups; a stratified approach being able to develop a deeper mechanistic understanding of these sub-groups, thereby aiding the identification of novel targets and therapeutic strategies. The goal of stratified medicine should be to increase the number of effective therapy options rather than being limited to the discovery of biomarkers able to identify patients who are unlikely to benefit from available options. Such a focus could help address patient concerns that stratified medicine may be used to limit access to drugs.

In designing stratified studies, consideration needs to be given to the need for partnerships, the range of therapies to be assessed, and the design of trials:

- Partnerships between clinicians, lab scientists, industry and patients are critical for the success of stratified medicine studies. The instigator of such partnerships can be either industry, academia or be catalysed by patient groups.
- Patients are interested in receiving the best therapeutic option for them not in whether they will or will not respond to an individual company's drug. To address this question requires the assessment of panels of therapeutic options.
- Novel trial designs are able to assess multiple treatments and biomarkers simultaneously. In such trials, the drug and biomarker can be developed in parallel with the trial based on initial hypothesis and adapted to information as it emerges.

Future stratified medicine opportunities include deeper stratification, broadening the range of disease focused consortia and addressing common challenges:

- Deeper stratification would seek to capture more of the patient complexity, through the inclusion of environmental factors, behavioural analysis, mental health status, the microbiome, etc.
- The portfolio of supported consortia might be enlarged by including diseases with rich pharmacology, enabling multiple disease pathways to be probed, and diseases regarded as being ripe for stratification such as asthma, inflammatory bowel disease, cancers and pain.
- A cross cutting approach could be taken to address common methodological, data and skill set needs:
 - o Stratified medicine poses novel methodological and statistical challenges in defining responders and selecting patient groups for study. In addition, new statistical tools are required to support biomarker discovery, validation, clinical utility and health economic studies.
 - o Managing and analysing the diversity and volume of data generated in stratified medicine studies poses significant challenges and opportunities. Tackling these issues through the development of standards and potentially common platforms could allow the pooling of data across disease areas, thereby enabling the development of a new taxonomy of disease based on differences in underlying pathobiology.
 - o If stratified medicine is to succeed, there is a need to train health care professionals in medical informatics and omics and to address the paucity of research pathologists. The MRC's stratified medicine consortia could provide valuable platforms to help meet these training needs and thereby help secure their longevity.

1. MRC Stratified Medicine Strategy Workshop

The MRC held a stratified medicine strategy workshop in London on 4th July 2013, to consider how the field's opportunities and needs had developed since the development of its initial strategy in 2011.

The aim of the workshop was to

- provide an overview of MRC and other public and charitable activity in the field, to assist attendees identify possible opportunities/gaps in support
- to reflect on scientific progress since the MRC first developed its stratified medicine strategy, assisted by presentations from EU and US academic and industrial leaders, to help ascertain UK strategic requirements to ensure it retains its leading position; and
- to consider the opportunities and challenges faced by those undertaking stratified medicine research, to help identify what practitioners require in order to best exploit a stratified approach

This report presents the background to the workshop, its recommendations and a synopsis of presentations.

2. Stratified Medicine

Stratified medicine is based on identifying key sub-groups of patients with distinct endotypes, these being distinguishable groups with differing mechanisms of disease, or particular responses to treatments. Stratification allows targeting of treatments to specific disease pathways, identification of treatments effective for particular groups of patients, and co-development of diagnostics to ensure the right patient gets the right treatment at the right time. Stratification can be used to improve mechanistic understanding of disease processes and enable: the identification of new targets for treatments; the development of biomarkers for disease progression and response to treatment; and novel treatments to be tested in the most appropriate patient groups.

Stratified medicine is a major component of the MRC's research strategy, with a commitment to invest £60m over the current spending review period. The MRC is coordinating action in this area with the Technology Strategy Board (TSB), the National Institute of Health Research, the UK Health Departments, Cancer Research UK (CRUK) and Arthritis Research UK.

3. The MRC's Stratified Medicine for Patient Benefit Initiative

In 2011, following extensive discussion with key stakeholders, the MRC has adopted a disease-focussed approach to its stratification for patient benefit initiative, building on experience gained in the establishment of three large scale academic/industrial consortia (detailed in [Annex 1](#)) under the MRC/ABPI Inflammation and Immunity (I&I) programme.

In the initiative's first call, held in 2012, we helped develop and fund UK-wide research consortia each focussed on a specific disease area, priority being given to proposals that focused on diseases with an existing therapy or therapies to which patients were known to differentially respond. The call's first three awards were announced in December 2012 and a further award was announced in June 2013. These awards totalled c. £16 million and were made to consortia targeting rheumatoid arthritis, hepatitis C, a rare genetic condition called Gaucher's disease and primary biliary cirrhosis (detailed in [Annex 1](#)).

Disease areas without existing therapy options can also benefit from a stratified approach. In recognition of this and because of the significant medical and societal challenges posed by age-related neurodegenerative diseases, in 2013 the MRC launched a call to create a UK Dementias Research Platform under the stratified medicine initiative. The Platform will be used initially to record in a systematic way the progression of neurodegeneration according to age and physiological variables and to identify surrogate markers with functional readouts.

Subsequently this information will form the basis on which to stratify patient groups for new therapeutic approaches.

Due to the field being new, both to applicants and the MRC, we have taken an iterative and supportive approach to the development and assessment of submissions; this has helped us together better define the key characteristics of strong submissions and consortia (see [Annex 2](#)). We are also investing in complementary activities including methodology research hubs, to develop new tools to support stratification, medical bioinformatics, to develop infrastructure and tools for integrating and analysing data, and high-throughput science, to make best use of cohort studies, tissue resources and animal model collections (see [Annex 3](#)). In addition to the lessons we have learnt, work by groups in the US (the National Research Council's "[Toward Precision Medicine](#)" report) and Europe (the European Science Foundation's "[Personalised Medicine for the European Citizen](#)" report) has further highlighted strategic opportunities and challenges presented by taking a stratified medicine approach.

4. Strategy Workshop

In light of these recent developments and with a growing appreciation of the complexities of undertaking inherently multi-disciplinary, multi-institutional research, the MRC felt it timely to bring field participants together in a Strategy Workshop. This workshop sought to consider how the field's opportunities and needs had developed, with the goal of considering whether and how the MRC's stratified medicine strategy, developed in 2011, might need amending, so as to keep the UK at the forefront of this rapidly developing field.

The Workshop agenda (see [Annex 4](#)) included talks from funders, academia and industry who together provided perspectives from the United Kingdom, Europe and the United States. The presentations, summarised in [Annex 5](#), were followed by open discussions, co-chaired by Professor Sir John Savill, MRC CEO, and Professor Patrick Johnston, Queen's College Belfast and Chair of the MRC Stratified Medicine Steering Group. These discussions led to the following recommendations.

5. Workshop Recommendations

5.1. The Goal of Stratified Medicine

By providing deeper mechanistic understanding, stratified medicine has the potential to improve patient outcomes.

Professor Stephen Holgate (University of Southampton) described how improved molecular understanding of disease is already delivering patient benefit. A growing understanding of the genetic mutations driving Cystic Fibrosis has enabled the development of drugs targeting specific genotypes. Targeted interventions such as these make it likely that medicine will move from being a reactive to a proactive discipline over the next decades; one that is predictive and personalised.

Professor Paul-Peter Tak (GlaxoSmithKline) presented a case study from his work on Rheumatoid Arthritis where the mechanistic insights derived from biomarkers identified through stratification studies can enable the development of more robust treatment algorithms, even when these biomarkers are not sufficiently predictive to be applied on an individual basis.

Professor Max Parmer (MRC Clinical Trials Unit) suggested that the poor efficacy observed in many Phase III trials, might be due to the drowning out of a signal from an unknown sub-group of patients. By identifying this sub-group, we might increase the positivity rate. Professor Parmer recommended, however, that, if all we do is pull out the poor responders, we will not increase benefit to the whole population. Although biomarkers are promising, what is needed are new effective treatments. Professor Tak explained that the old model of selling a drug to all comers is not supportable ethically or commercially. There is a need to make a more compelling story and for this efficacy is key.

It was recommended that the goal of stratified medicine should be to increase the pool of efficacious and safe drugs. To achieve this it is necessary to recognize that diseases are syndromes existing of different pathobiological sub-groups; a stratified approach being used to develop a deeper mechanistic understanding of these sub-groups, thereby aiding the identification of novel targets and therapeutic strategies. Such a focus could help address patient concerns that stratified medicine may be used to limit access to drugs.

5.2. Study Design

5.2.1. Collaboration

Professor John Isaacs (University of Newcastle) explained how partnerships between clinicians, lab scientists, industry and patients are critical for the success of stratified medicine studies and that the input of these multiple stakeholders is needed from the planning stage. Industry partnership provides necessary access to new therapies and to good pharmacokinetic and pharmacodynamic measures.

Mr Tim Pitfield (Janssen Diagnostics) recommended that there may be a need to increase awareness in the diagnostic industry of the opportunities emerging from MRC supported activity. He questioned however whether incumbent players might have the right resources to best capture these opportunities, given that they remain, in general, focused on traditional diagnostics (haematology, blood chemistry, etc).

The instigator of stratified medicine partnerships can be either industry or academia or catalysed by patient and charity groups. Dr Ian Walker (Cancer Research UK) described their stratified medicine programme, the first phase of which has been a collaborative initiative to undertake large volume genetic testing within the UK. This has required the establishment of a single network consisting of 26 feeder hospitals, with 8 clinical and 3 technology hubs, which to date has collected 7,962 samples for testing and undertaken 34,375 genetic tests

To attract industry partners, academics need to develop a clear message of the benefits they offer and build strong contacts with research teams in industry. Dr Ellie Barnes (University of Oxford) noted that building such relationships can be difficult, as identifying the correct industry contacts is not straightforward, and these relationships are very different to the classic consultant/industry relationships.

Although agreeing that collaboration is critical, participants cautioned that there exist perverse incentives in academia, such as the diluted recognition associated with contribution to multi-author publications, which can work against this.

5.2.2 Hypothesis Led

While a hypothesis led approach has benefits in justifying the deployment of limited resources, it was proposed that there may also be merit in hypothesis free approaches. Professor Issacs explained how, in rheumatoid arthritis it is known that the response to methotrexate varies between patients and by the stage of disease. Currently, however, there is no hypothesis to explain this. In such cases, an open discovery approach could be valid. Such an approach would likely benefit from a clearly argued case setting out the reasons for why particular sources of biomarkers (e.g. RNA derived from affected tissues, circulating proteins, etc) have been selected for investigation and a strategy for how promising avenues will be identified and prioritized for study.

5.2.3 Panels of Therapeutic Options

Patients are interested in receiving the best therapeutic option for them and not in whether they will or will not respond to an individual company's drug. To address this question requires the assessment of panels of therapeutic options.

Professor Max Parmer described novel trial designs that are able to assess many treatments and biomarkers in parallel and include all recruited patients. Professor Parmer argued that you cannot wait for a fully validated biomarker before developing the treatment or visa-versa. The drug and biomarker need to be developed in parallel with trial design based on initial

hypothesis and then adapted to information as it emerges both within and without the trial. Professor Tak presented a model in which you build a stratification rationale pre-clinically, collate evidence in Phase I/IIa, test your hypothesis in Phase IIB, and then co-develop the drug and companion diagnostic in Phase III.

The review of panels of therapeutic options poses challenges, as this will likely require consortia to seek contributions from multiple industrial partners, given that no individual company will likely be working on all possible pathways. While gaining access to pre-licensed products for use in comparative studies can be challenging, the oncology field is moving in this direction. Industry recognizes that it cannot explore all of the opportunities and that sharing risk with academia is one way forward. The MRC might explore the roll out of such models beyond cancer.

5.3 Future Opportunities

5.3.1 Deep Stratification

Future stratified medicine opportunities might include deeper stratification, capturing more of the patient complexity, through the inclusion of environmental factors, behavioural analysis, mental health status, the microbiome, the effect of existing drugs etc.

Professor Holgate emphasized the unique opportunity presented by the world leading Phenome Centre. The Centre, part of the Olympic legacy, is jointly funded by NIHR, MRC and industry and is focused on examining population variation of the metabolome. While the metabolome has been shown to be a potential stratification tool, for example in predicting the progression risk of hepatitis to hepatocellular carcinoma, stratified medicine is not currently within the Centre's remit.

Professor David Goldstein (Duke University) proposed that clinical trials offer a platform for studies investigating genetic drivers of differential response but that the genomic arms of such trials, where they exist, are not generally undertaken to fully contemporary standards. Such studies could therefore provide a good opportunity for productive academic/commercial partnership.

5.3.2 Range of Disease Focused Consortia

The disease focus adopted by the MRC in its initial strategy was supported by participants with areas for further development potentially including diseases with rich pharmacology, enabling multiple disease pathways to be probed, or diseases ripe for stratification, which participants proposed might include asthma, inflammatory bowel disease, cancers and pain. Collaborative opportunities exist where these disease overlap with the NHS infrastructural investments in, for instance, Translational Research Partnerships.

5.3.3 Common Challenges

A cross cutting approach could be taken to address the common methodology, data and skill set challenges facing stratified medicine consortia.

Methodology

Stratified medicine poses novel methodological and statistical challenges in defining responders and selecting patient groups to study. In addition, new statistical tools are required to support biomarker discovery, validation, clinical utility and health economic studies.

Professor Isaacs explained that, in order to identify biomarkers of response, you need clear measures of response. While objective measures are better than subjective ones, key measures in rheumatoid arthritis, such as pain, are subjective. The choice of outcome measures also varies depending on their use. NICE looks at quality of life outcomes. While, for patients, patient reported outcomes are critical.

In addition to selecting appropriate response criteria, you need to select your study population. If this population is too homogenous then you may not have sufficient diversity for the signal (differential response to drug) to emerge. Conversely too much diversity and the signal may

get drowned out. It is also necessary to recognize the complexity of having to deal with issues such as non-compliance and, in the context of biological drugs, immunogenicity.

Dr Mark Samuels (National Institute of Health Research), described the Diagnostic Evidence Centres recently established by the NIHR which seek to help develop the clinical utility, validity, and health economics evidence needed by commissioners to implement new diagnostic tools. Dr Samuels commented that there remains a gap in the methodological approaches required to robustly assess diagnostic tools, as they move down their development path.

Data

Managing and analysing the diversity and volume of data generated in stratified medicine studies poses significant challenges and opportunities.

Professor Holgate commented that the debate in US and here is whether we develop a new taxonomy of disease that defines disease based on underlying molecular and environmental causes. This will require the creation of an "Information Commons", a data repository that links layers of molecular data, medical histories, including information on social and physical environments, and health outcomes to individual patients. The creation of such a commons is currently hampered by the lack of a shared language between clinicians, biologists and industry; a situation that is compounded by the need to bring in additional expertise, including mathematical and sociological, with more challenging language differences.

Dr Ian Dix (AstraZeneca) noted that projects routinely underestimate the efforts required in data management and that this challenge is mainly a service rather a research challenge that does not necessarily fit well with research funding models. Support for service functions potentially requiring different assessment and monitoring criteria.

Dr Dix proposed that an absence of standards leads to poor interoperability and results in islands of data, complicating data discoverability, mining and archiving. He proposed that the development of a national strategy addressing this issue could be beneficial and recommended that this should not seek to standardise everything. Rather there are some aspects, such as data management and sample tracking, which are likely areas for standardization and others, such as data capture and analytics, where you would desire more flexibility. The adoption of standards and potentially common data platforms could aid data sharing and archiving and help drive entrepreneurial business models producing new plug-in analytical tools and delivering support services.

While there are a number of initiatives in the UK focused on the data challenge, it was not clear to participants whether these are being optimally co-ordinated.

Training

Participants agreed that for stratified medicine to succeed, there is a need to train health care professionals in the opportunities presented by stratified medicine and in medical informatics and omics, so that they are able to support the field's development and implementation, and a need to address the paucity of research pathologists. It was suggested that the MRC's stratified medicine consortia could provide valuable platforms for addressing these training needs and that in doing so they could help secure their longevity.

6. Annexes

Annex 1 – Supported Consortia

Annex 2 – Lessons Learnt

Annex 3 – Complementary MRC Activities

Annex 4 – Workshop Agenda and Attendees

Annex 5 – Workshop Presentations

Annex 1 – Supported Consortia

1. MRC/ABPI Inflammation and Immunity Initiative

The MRC's Stratified Medicine initiative has drawn on experience gained through investment in three pilot consortia – in Chronic Obstructive Pulmonary Disease (COPD), rheumatoid arthritis and diabetes, under the MRC/ABPI Inflammation and Immunity Initiative.

1.1. The COPD MRC/ABPI Partnership (COPD MAP)

COPD MAP is building a number of hypothesis driven research questions around a federation of COPD cohorts. The aim is to get a holistic view of disease progression - all studies to be conducted on the same patient samples/groups with full clinical history and phenotypes with data being shared across all partners in real time. Key areas for research include understanding the patients more deeply, investigating the exacerbation of symptoms after infection, identifying new disease mechanisms as drug targets or biomarkers and understanding the mechanisms underlying the muscle wasting associated with COPD.

1.2. The Rheumatoid Arthritis Consortium

Aims to investigate two aspects of the disease, the first through the TACERA study - towards a cure for early rheumatoid arthritis –a longitudinal observational study of patients with early RA. This will be coupled to developing an “immune toolkit” to identify the immunological changes that occur as early disease develops into more chronic rheumatoid arthritis.

1.3. MRC APBI Stratification and Extreme Response Mechanism IN Diabetes (MASTERMIND)

The mission of the MASTERMIND consortium is to establish a platform for a stratified medicines approach to the treatment of type 2 diabetes to act as a springboard for future research and development by academia and industry.

2. Stratified Medicine Consortia Awards

The initiatives first consortia awards, totalling c. £16m, were made to four consortia targeting rheumatoid arthritis, hepatitis C, a rare genetic condition called Gaucher disease, and primary biliary cirrhosis.

2.1. STOP-HCV

A hepatitis C consortium, led by the University of Oxford, will develop cutting-edge gene sequencing technologies to find out why 30 per cent of people fail to respond to a new type of hepatitis treatment called direct antiviral therapy. The group of 14 academic institutions and eight industry partners will use a state-of-the-art clinical database and a bio-repository of blood samples from hepatitis C infected people that has been established by HCV Research UK — a multi-disciplinary collaborative enterprise funded by a £1.92m grant from the Medical Research Foundation and based at the MRC-University of Glasgow Centre for Virus Research. This information will help the STOP-HCV consortium to decipher the genetic makeup of both the virus and the patient and draw this information together to improve patient care.

2.2. MATURA

Supported in partnership with Arthritis Research UK, the MATURA consortium, led by Queen Mary, University of London, and the University of Manchester, aims to enable early, effective treatment and improve the cost-effectiveness of care for around 500,000 people in the UK who suffer from the painful inflammatory condition rheumatoid arthritis. It will search for biological and genetic markers in blood and joints which could be used as clues to predict how patients will respond to disease-modifying drugs. If successful it is estimated that a stratified treatment approach for this condition could save the NHS £13-18m a year. Co-funded by a £1m grant

from Arthritis Research UK, this project combines 12 academic groups with nine industry partners.

2.3. The GAUCHERITE consortium

Aims to improve the care of people with Gaucher, a rare genetic disorder in which a build-up of fatty chemicals causes bleeding, painful skeletal complaints and swelling of some internal organs. Even identical twins differ markedly in disease severity, indicating that non-genetic components play a role in the condition. Five treatments are currently available, but patients could respond differently to drugs because of the complexity of the disease. GAUCHERITE will bring together specialist doctors and scientists, led by Cambridge University, who will examine at least 85 per cent of all UK Gaucher patients and 'stratify' them by the nature of their disease to allow them to better target therapy interventions. They will also work closely with major industrial partners and patient groups.

2.4 UK-PBC

Primary Biliary Cirrhosis (PBC) is thought to affect 20,000 people in the UK – currently, around 30% of patients with this condition do not respond to the only drug treatments available and their only option is a transplant. The new UK-PBC consortium led by Newcastle University and funded by a c. £4.8m award from the MRC will recruit half of those affected in the UK, 10,000, at sites around the country. This new collaboration, between scientists, doctors and patient groups, will provide a better understanding of why some patients respond to treatment and some don't; work with pharmaceutical companies to develop new drugs; and design a national protocol to streamline treatment across the UK. This will help ensure that, in future, patients receive the right type and level of treatment depending on the severity of their disease and individual biological make-up, and determine whether that should be at their GP or in a specialist centre.

Annex 2 – Lessons Learnt

In the assessment of submissions to the first call of the MRC's Stratified Medicine Initiative for UK-wide research consortia, the following lessons emerged regarding the features of strong proposals:

- Proposals should be focused on stratification by response (theragnostics). Stratification by risk, diagnosis and/or prognosis alone not being in scope.
- Proposals should be simple and effective. They need to have clarity of vision and science. They should be challenging, while not attempting to do too much.
- In the future, diseases are likely to be classified by mechanism rather than clinical presentation
 - o Stratification strategies focused on identifying groups of patients with distinct endotypes (subtypes of a condition defined by a distinct functional or pathobiological mechanism) where favoured.
 - A patient may traverse more than one endotype during the course of their disease
 - Biomarker discovery/validation should optimally be linked to mechanistic workpackage(s) to further the understanding of disease processes and/or pharmacology. The endotype can help provide this linkage.
- The Panel did not favour fishing trips. Proposals should be based on, clearly present and then propose to test/expand a molecular mechanism/hypothesis able to account for the observed differences in patient response
 - o In developing underpinning hypothesis, it is important to consider both disease and pharmacological drivers.
 - Many proposals were weak on the latter, both in terms of their rationale and execution.
 - In the submission, it can be helpful to provide a critique of pharmacological deficiencies of current drugs.
 - In the delivery phase, it may be important to consider whether
 - » sample collection protocols capture pharmacologically relevant data (e.g. time from last dose, strength of dose, etc.)
 - » relevant details of adverse events are appropriately captured
 - Consideration should also be given to the potential roles of co morbidities and/or overlapping disease pathways.
 - o The inclusion of xxxomic studies lacking a strong rationale and robust and appropriately powered studies weakened proposals.
- It is important that proof of concept data be provided supporting the hypothesis to be tested and the approach being taken. If this data has not been published, it should be included within the submission.
- The consortium should seek to develop a set of synergistic workpackages, with appropriate governance structures and PI time commitment, able to provide a balanced portfolio of outputs, which might include
 - o Short term – e.g. identification of clinical trial study groups with expected cleaner response
 - o Medium term – e.g. identification of diagnostic tools able to guide clinical decision making
 - o Longer term – e.g. better understanding of drug pharmacology/disease mechanisms that could in turn inform new therapy developments

In addition, applicants should helpfully give consideration to

- Patient involvement/engagement – while stratified medicine has patients at its heart, it relies on their goodwill and participation for its success. The involvement of patients during both the planning and execution phases is therefore of critical importance. While representatives from relevant health charities can provide helpful input, it may also be worth including other patient perspectives, particularly from those who you plan to engage in studies.

- o True partnership with patients can help manage potential concerns that stratification could lead to exclusion from treatment; a particular pertinent issue in diseases with limited therapy options.
- Industrial participation – prototypical consortia are advised to engage with industry earlier rather than later, to better enable the development of mutually beneficial plans
- Need for development of clinical descriptors in line with biomarker studies for both disease classification and drug response. If descriptors are weak, starting group definitions will be weak, making biomarker discovery more difficult
- Use of adaptive screens to identify and prioritize drivers of variability
- The development, in collaboration with clinical colleagues, of estimates of the diagnostic power required from a test used to direct therapy choice, if it is to impact clinical decision making. Such estimates can help in study design.
- Compliance/concordance. Is a lack of response due to a lack of drug in the system
- Consortium durability - once established how will platform be maintained over what might be 10-15 year span if it is to inform mechanism, then back translate to new targets/drugs.
 - o Do not look solely at interventions in current use but also at those coming down the pipeline. Present the portfolio of emerging interventions and the consortium's plans for engaging with these.
- How the different data types collected will be stored and shared both within the consortium and more widely.
 - o Are there aligned initiatives underway or planned elsewhere? Could the consortium's impact be enhanced by ensuring data compatibility between initiatives? Might additional complementary measurements from those planned be captured that could enhance the value of the consortium's data to the field?

Annex 3 – Complementary MRC Activities

1. Hubs and Network for Trials Methodology Research

MRC's Hubs in Trials Methodology Research were established in 2008, with 5 years funding at ~£17.5m, with the aim of supporting the development of trials methodology research in the UK. MRC supported 8 hubs – 5 University based (Belfast, Birmingham, Bristol, Edinburgh and Liverpool) and 3 based in MRC Units (Biostatistics Unit (BSU) -Cambridge, Clinical Trials Unit (CTU)- London and the Clinical Trials Service Unit (CTSU) - Oxford) – with an associated network (see <http://www.methodologyhubs.mrc.ac.uk/>).

Key themes being addressed by the hubs include:

- Adaptive Designs
- Evidence Synthesis
- Stratified Medicine
- Trial Conduct and Recruitment
- Outcomes

The Network was funded to facilitate collaborative methodological research and to enable a concerted approach to the implementation of the most effective methods relevant to trials.

In April 2013, the MRC agreed to provide continued support to two of the five University hubs, Bristol and Liverpool, along with the Hub Network, to a total of £7.5m. There was also a commitment to continue to support the development of the hub in Northern Ireland. Going forward, funding for the three unit hubs will be embedded in their core unit budgets.

2. Medical Bioinformatics

2.1. MRC Vision and Strategy in Medical Bioinformatics

Enormous research gains and significant advances in medicine and public health can be derived from integrating, analysing, and interpreting the array of information within NHS clinical records, health research, rich biological data, imaging and routine administrative data. MRC's vision is to harness the vast sources of biological, clinical, population and environmental data to gain new scientific insights and significant population health benefits from large scale analysis and integration of complex datasets.

There are five strategic elements supported by MRC investments that underpin the vision of discovery science from diverse datasets in safe environments that protect privacy and confidentiality:

- Infrastructure and resources to enable data collection, curation and storage
- Policies to encourage data discovery, safe access and data sharing
- Trusted research environments with appropriate governance and policy frameworks that protect patient and research participant confidentiality – safe data in safe havens
- Building capacity and careers in important skills for analysing large and complex data such as bioinformatics, biostatistics, population health sciences, methodology research and interdisciplinary social and biomedical sciences.
- Supporting enabling technologies and infrastructures that allow secure storage, sharing, analysis and linkage.

2.2. Funding for Medical Bioinformatics Research

Over a 12 month period the MRC is investing in **£90m** in partnership with government and charity funders, on a number of high profile initiatives to implement key parts of the MRC Strategy for Medical Bioinformatics. The initiatives are focused on analysing and linking patient records and health research data, and integrating clinical and population data with rich biomedical data. Together these activities will boost UK informatics research, build essential

skills and capacity and provide the enabling technologies and infrastructure for research at scale.

2.2.1. eHealth Informatics Research Centres (eHIRCs)

- In 2012 the MRC brought together a consortium of ten funders to establish ehealth informatics research centres across the UK. The aim of the eHIRCs is to undertake research linking e-health records with other forms of health research and routinely collected data in safe data environments.
- £19m was awarded to four eHIRCs based at UCL London, Manchester, Swansea and Dundee. Together the eHIRCs involve a total of 19 UK universities and 2 MRC Units.
- A key objective of the eHIRCs will be to build capacity in skills linking complex large datasets by offering interdisciplinary career development and training opportunities across biomedical, social and computer sciences.
- To add value to the eHIRC initiative a UK health informatics research network is being established to harness expertise in the wider UK research community, develop methodologies, share best practice, provide a central route for collaborating with industry, the NHS and policy and play an important role engaging the public to promote the benefits of using health records in research.
- The eHIRCs and network were officially launched at the MRC sponsored e-health informatics research conference on 1st May 2013.

2.2.2. £20m additional capital investment in eHIRCs

- To further strengthen the UK's capability in interpreting complex health datasets, in May 2013 the MRC invested an additional £20m capital funds into the eHIRCS.
- The additional funds will be used to create a virtual health informatics research institute that builds on the existing scientific programmes in the eHIRCs. Funds will co-locate eHIRC researches with NHS staff and other stakeholders, increase access to clinical and population databases for research, extend partnerships with the NHS, industry and academia and create digital infrastructures to safely share health datasets across regional boundaries.

2.2.3. £50m Medical Bioinformatics call

- In March 2013, the MRC launched a call for expressions of interest in Medical Bioinformatics – building capability, capacity and infrastructure. The Initiative will strategically invest £50m (£35m capital and £15m resource) to improve linkage and analysis of large-scale omics and complex phenotypic data with clinical and population health data, provide infrastructures and tools, and support skills/career development to improve understanding of human disease.
- In May 2013, an Expert Steering Group shortlisted 12 applications for further consideration. Final funding decisions will be made in November 2013. MRC expects to award up to 6 major strategic awards which will be innovative and diverse, but which will coordinate effectively and contribute to medical research in the UK across institutions, academia, the NHS and industry.

3. High Throughput Science Call

This call aims to take advantage of the new technologies in high throughput science to significantly enhance existing, high-value MRC investments. For the purposes of this call, high throughput science encompasses 'omics (e.g. genomics, metabolomics, transcriptomics), imaging, and cellular assays. Investments will be targeted at MRC-funded cohort studies, tissue resources and animal model collections, or those that are funded by others but which are central to the MRC-funded research activities within MRC Units, Centres or Institutes. The activities will produce large and complex data sets and to maximise major, long-term impact there will need to be robust strategies for collection, curation and access (including from the wider scientific community).

Annex 4 - Workshop Agenda and Attendees

4th July 2013

BIS Conference Centre, 1 Victoria Street, London, SW1H 0ET

10:00 Chairs Welcome (5 mins)

10:05 Scene Setting (40 mins)

MRC Presentation (15 mins)

- Definition of Strat Med and overview of UK landscape and where MRC sits
- What MRC has sought to achieve
- What we have done and learnt thus far

Technology Strategy Board Strat Med activities (8 mins)

NIHR Strat Med activities (8 mins)

Cancer Research UK Strat Med activities (8 mins)

10:45 Academic Industry Perspectives (EU and US) (1hr)

Mix of academic and industry perspectives (Stephen Holgate (European view) Paul-Peter Tak (Pharma view); Tim Pitfield (Diagnostics view); David Goldstein (US view)) on what the field offers and needs (4 x 15 min presentations)

11:45 Coffee break

12:00 Open discussion (30 mins)

UK strategic opportunities and needs; **agree two topics for further discussion in afternoon**

12:30 Lunch

13:15 Exploiting the Opportunity (1hr)

Examples of Strat Med work from practitioners with goal of highlighting areas of opportunity and needs for implementation (4 x 15 min presentations)

- Science of Strat Med Consortia – to include balance of theragnostics versus mechanistic work (MRC Consortia leads – John Isaacs; Ellie Barnes)
- Stratified Trials (Max Parmar, MRC CTU)
- Data Platforms and Mining (Ian Dix, AstraZeneca)

14:15 Open discussion (30 mins)

Practical opportunities and needs; **agree two topics for further discussion in afternoon**

14:45 Coffee break

15:00 Chaired discussion of 4 topics agreed for further debate (40 mins, c. 10 mins each)

15:40 Summation, advice for MRC (20 mins)

- Types of initiatives required
- Focus of MRC activity
 - o Disease led/Therapy led
 - o Extent of mechanistic studies
 - o Optimal time and means to engage with industrial partners (pre-clinical, ph I, II, III, post MAA), etc

16:00 Close

Workshop Attendees

Name	Affiliation
Dr Eleanor Barnes	University of Oxford
Professor Anne Barton	The University of Manchester
Dr Mark Bechter	Chiesi Group
Professor Chris Brightling	University of Leicester
Professor Tim Cox	University of Cambridge
Dr Ian Dix	AstraZeneca
Dr Tom Foulkes	MRC
Dr Alasdair Gaw	Technology Strategy Board
Professor David Goldstein	Duke University
Professor Andrew Hattersley	University of Exeter
Professor Harry Hemingway	University College London
Professor Stephen Holgate	University of Southampton
Professor Edward Holmes	Biomedical Research Council, A*STAR, Singapore
Professor John Isaacs	Newcastle University
Ms Hannah Isom	MRC
Professor Paddy Johnston	Queen's University, Belfast
Professor Dave Jones	Newcastle University
Dr Andrea Jorgensen	University of Liverpool
Professor Debbie Lawlor	University of Bristol
Dr Louise Leong	ABPI
Mrs Mirella Marlow	NICE
Dr Declan Mulkeen	MRC
Professor Jackie Oldham	The University of Manchester
Professor Kevin Park	University of Liverpool
Professor Max Parmar	MRC Clinical Trials Unit
Dr Jonathan Pearce	MRC
Professor Hugh Perry	University of Southampton
Mr Tim Pitfield	Janssen Diagnostics
Professor Costantino Pitzalis	Queen Mary, University of London
Dr Mark Samuels	NOCRI
Professor John Savill	MRC
Professor Alan Silman	Arthritis Research UK
Dr John Stageman	Independent
Professor Paul-Peter Tak	GlaxoSmithKline
Professor Jeremy Tavare	University of Bristol
Professor Rajesh Thakker	University of Oxford
Dr Brian Tom	MRC Biostatistics Unit
Dr Chris Torrance	Horizon Discovery
Professor Tjeerd-Pieter van Staa	CPRD
Dr Ian Walker	Cancer Research UK
Dr Des Walsh	MRC
Dr Jean Waters	MRC Public Panel
Dr Neil Weir	UCB
Dr Penny Wilson	Technology Strategy Board

Annex 5 – Workshop Presentations

The workshop was arranged in three sessions (agenda and attendees included as [Annex 4](#)).

1 Scene Setting

The aim of this session was to provide an overview of MRC and other public and charitable activity in the field was provided, to assist attendees identify possible opportunities/gaps in support.

Des Walsh (MRC) presented the MRC's current strategic approach to stratified medicine, which builds on the MRC/APBI MRC/ABPI I&I programme and is supporting disease focused consortia targeting conditions with existing interventions having known differential response.

Dr Alasdair Gaw (TSB) highlighted the strategic aims of the TSB, which include supporting innovation and growth of UK industry and accelerating product development from concept to commercialisation. The TSB's Stratified Medicine Innovation Platform seeks to bring together the best of British academia and industry, to create innovative solutions, and to enable the acceptance and implementation of stratified medicine in the UK. Key field needs identified through a TSB led road mapping exercise include incentivisation of adoption, increasing awareness, challenges in conducting clinical studies and trials, data collection, management and use, biobanks, regulation and intellectual property. To help address these needs, the TSB is committing up to £50m in programmes that have included the development of stratified medicine business models and the health economic analyses of diagnostic tools able to predict adverse effects and non-responders. Planned initiatives include calls for enabling clinical imaging and cell analysis technology for stratification, with consideration also being given to future initiatives in neurodegeneration and diabetes.

Dr Mark Samuels (NOCRI) outlined the challenge of getting new diagnostics to patients due to a lack of clinical validity, utility and health economics evidence needed by commissioners. To help build this necessary evidence base, the National Institute of Health Research has established four Diagnostic Evidence Centres (DECs), which will be virtual centres with the required critical mass and breadth of skills and resources, including access to patients. It is hoped that the outputs of the DECs will be evidence ready diagnostics ready to be picked up either by NICE or directly by commissioners. It is anticipated that they will be of great benefit to the diagnostic's industry and the growth agenda.

Dr Ian Walker (CRUK) described CRUK's stratified medicine programme, the first phase of which has been a collaborative initiative to undertake large volume genetic testing within the UK; the aim being to test approximately 9000 patients in two years across the UK in real world NHS settings. This has required the establishment of a single network consisting of 26 feeder hospitals, with 8 clinical and 3 technology hubs, which to date has collected 7,962 samples for testing and undertaken 34,375 genetic tests. The network is supported contributions from the pharmaceutical industry (Pfizer and AstraZeneca), the Government (TSB and National Health Service), the Diagnostics (Roche and BMS) and Information Technology industry (Oracle). Operational collaboration has been critical for the network's success. However, the network has also identified a number of on-going challenges that include

- Establishing routine consent of data and samples for research
- Achieving clinically relevant turnaround times
- Data integration
- Establishing standards for sample handling, preparation and processing

Dr Walker then presented an overview of the second phase of CRUK's programme. The programme will focus on lung cancer patients and use a multiplexed approach to assess a panel of markers of at least 2,000 patients per year. The findings from these screens will be used to feed a National Matrix study of non-randomised design, with treatment allocation according to molecular phenotype. The study will be a national study open at all Experimental Cancer Medicine Centres and will be carried out under a single clinical trial protocol and

regulatory submission. This will ensure that patients are treated at their home sites rather than at a central study point.

2 Scientific Progress and UK Strategic Requirements

The aim of this session was to reflect on the strategic opportunity presented by stratified medicine, the strategic assets (people, resources and infrastructure) that it requires and the potential gaps in the UK's provision of these assets. While biased towards the MRC's scope, which extends from discovery through establishing clinical proof of concept, it was recognized that MRC's strategy should be informed by a holistic view, so as to increase the likelihood of MRC research reaching and having impact in the clinic.

Professor Stephen Holgate (University of Southampton) described how our improved molecular understanding of disease is already delivering patient benefit. While cystic fibrosis (CF) is regarded as a single gene disease, it arises from over 1,500 distinct mutations in the CF transmembrane conductance regulator (CFTR) gene. The third most commonly found mutation G551D is found in c. 4% of CF patients, but has a much higher prevalence of c. 20% in Ireland. Vertex is developing a drug (VX-809) which, in initial trials, has been shown to elicit a beneficial change in lung function within 15 days; by improving the transport of the G551D mutated CFTR protein to the lung cell surface. Targeted interventions such as this make it likely that medicine will move from being a reactive to a proactive discipline over the next decades; one that is predictive and personalised.

To better understand the impacts and needs of this development, the European Science Foundation (ESF) has undertaken an analysis of 'Personalised Medicine for the European Citizen: Towards more precise medicine for the diagnosis, treatment and prevention of disease'. This review highlighted the need for better public and health authority understanding of what stratified medicine is and what it might deliver. Addressing this in the UK will likely require engagement with other research communities and research councils. The biggest hurdle identified by the ESF review was the difficulty of bringing together and integrating all the data necessary to develop a stratified approach. Such data may come from different sources and be in different formats. The debate in US and here is whether we develop a new taxonomy of disease that defines disease based on underlying molecular and environmental causes. This will require the creation of an "Information Commons", a data repository that links layers of molecular data, medical histories, including information on social and physical environments, and health outcomes to individual patients. The creation of such a commons is currently hampered by the lack of a shared language between clinicians, biologists and industry; a situation that is compounded by the need to bring in additional expertise, including mathematical and sociological, with more challenging language differences.

Turning to stratified medicine's infrastructure needs, Professor Holgate emphasized the unique opportunity presented by the world leading Phenome Centre. The centre, part of the Olympic legacy, is jointly funded by NIHR, MRC and industry and is focused on examining population variation of the metabolome. While the metabolome has been shown to be a potential stratification tool, for example in predicting the progression risk of hepatitis to hepatocellular carcinoma, stratified medicine is not currently within the Centre's remit.

Professor Paul-Peter Tak (GlaxoSmithKline) outlined the treatment algorithm for rheumatoid arthritis, in which patients are started on conventional steroids, with non-responders being moved onto more expensive biological therapies, which themselves have a range of responses. To identify potential predictors of response, responders and non-responders have been compared. While extensive omics studies have not identified strong predictors, TNF expression in synovial tissue was found to be a good predictor. Differences at the population level were highly significant. However, at the individual level there was substantial overlap. This is a common issue and limits the predictive power of the test.

The mechanistic insights this work provided did though enable the development of a more robust treatment algorithm. If a patient has failed a TNF blocker then they are less likely to respond to a second TNF blocker, as the disease is less likely to be TNF related, so try

targeting another mechanism of action. If, however, the patient did initially respond, then the loss of response may be due to an antibody reaction against the primary therapy, so a different anti-TNF agent might work. The development of this pathway has improved patient management, even in the absence of a new diagnostic tool.

This work has also shown that prediction of response can be improved by integrating different clinical, imaging and molecular markers.

The old model of selling a drug to all comers is not supportable ethically or commercially. There is a need to make a more compelling story and for this efficacy is key. To achieve this we have to recognize that diseases are syndromes consisting of different pathobiological sub-sets and that the classification of disease has been rather irrational, how many joints are affected, is it symmetrical, etc. This is not very scientific, what we need is to be able to link molecular mechanism to disease.

Turning to other disease areas that might benefit from a stratified approach, Professor Tak highlighted immune related diseases such as SLE, where more academic work is needed to better define the many different disease sub-groups. This is also true of for instance Crohn's disease, in which GSK has both late and early stage programmes.

To be most effective a stratified approach must be embedded in thinking from discovery forward. During the pre-clinical phase, a rationale for stratification must be developed. Evidence can then be built in phase I/IIa trials with hypotheses tested in phase IIb following which, if successful, the drug and companion diagnostic can be co-developed in phase III. GSK's experimental medicine gating criteria now include whether there is an understanding of patient populations who are more likely to respond.

Outstanding challenges include a need for more investment in disease stratification. In the UK, clinical trials can still pose a hurdle. Many centres in the UK being unable to deliver compared to centres in other countries. Finally, there is the challenge of the huge amount of data that will be collected and how this will be analysed.

Mr Tim Pitfield (Janssen Diagnostics) presented a personal view from the diagnostic industry of the challenges of adoption and implementation of stratified medicine in the National Health Service (NHS).

Diagnostics will have growing importance in the evolving healthcare marketplace with decentralization heightening its role in clinical decision making and diagnostic informatics consolidating patient data and transforming healthcare. A key driver is the growing importance of companion diagnostics to meet the need from patients, providers and payors for better, more cost-effective outcomes. While the therapeutic (Rx) is always the primary value driver, the companion diagnostic (CoDx) has entered as a secondary value driver. Modelling of the launch of Herceptin and its companion diagnostic, used to assess Human Epidermal Growth Factor Receptor 2 (HER2) protein overexpression, suggests that increased investment in the diagnostic launch strategy could have doubled cumulative Herceptin sales from c. £5.2bn to c. £10.9bn. An optimized strategy would have addressed the following issues:

- CoDx development not coordinated with Rx
- Only One CoDx company serving market at launch
- No CoDx market preparation in advance of Rx launch
- Propensity to prescribe not understood, measured or addressed

Optimized CoDx strategies can accelerate Rx market access and adoption, increase Rx market share, differentiation, and propensity to prescribe, and prolong the Rx lifecycle.

Adoption of diagnostics requires the development of an evidence base for technical feasibility, assay and clinical validity and clinical utility. Historically of lower importance, establishing clinical utility is becoming more critical but there is uncertainty as to how this will be assessed and the impact of this on adoption. Submissions to the NICE Diagnostic Assessment

Programme involve the mapping and possible redesign of patient pathways, which is very complex, and as analysis of cost effectiveness and clinical outcomes. While positive reviews can lead to the inclusion in NICE or equivalent guidelines, this may not be sufficient for mainstream adoption in the NHS.

If adoption can be achieved, the devil is in the detail when rolling out into the NHS. The evidence base was gathered in ideal conditions. However, the use of duplicate and triplicate measures may not be the model that is rolled out nationally due to funding issues. In addition, the model of delivery (centralized versus de-centralized) will likely be different in roll out versus how during evidence collection.

The use of “In House” testing can also have an impact on adoption. Although an in house test may be preferred, the true costs of such tests are not always captured. The costs can then prove unsustainable, if rolled out. Whichever test is used quality assurance is paramount.

Mr Pitfield was optimistic about the outlook for the diagnostics industry, more so than five years ago. Some of the hurdles are now well recognized and strategies, including the DECAs, are being put in place to address these. To aid adoption, industry should consider risk sharing models and embrace “in house” testing, maintaining the focus on quality and patient safety. Currently, however, industry remains focused on traditional diagnostics (haematology, blood chemistry, etc). Whether it has the right resources to move forward is an open question.

Professor David Goldstein (Duke University) presented examples of the power of genetics to stratify patients and provide new insights into the mechanistic drivers of disease.

It had been known for a long time that there was likely to be an important genetic component to the differential response to interferon treatment in Hep C. Using a genome-wide association study (GWAS), we identified a genetic variation of real and clear importance. Looking at EU ancestry, the cure rate in different genotypes ranged from 30% for those with the poor genotype to 80% for those with the good genotype. This was a good enough correlation that physicians ordered the test and used the results in their prescribing choices. Although the utility of this test has been attenuated by the introduction of new anti-virals, it highlights the opportunity of discovering genetic drivers of differential response. Clinical trials offer a platform for such studies. However, the genomic arms of such trials, where they exist, are, in general, not done to fully contemporary standards. This presents a good opportunity for productive academic/commercial partnership.

As well as being able to identify predictors of differential response, sequence analysis can be used to uncovering genetic causes of disease. Professor Goldstein presented recent work from the Epi4K Consortium examining the most extreme form of rare variants, de novo risk factors, in epileptic encapholohies. Everyone who runs sequencing studies ignores mutations in some genes and concentrates on others. When a stop mutation is found in an olfactory receptor it is ignored because we all have such stop codons, we therefore don't think such mutations have an effect. Currently the selection of which mutations to ignore is very informal. In this study, the team developed a method using the total variation in human genomes to predict clearly functional mutations. If in the population you have a gene that has an awful lot of functional variation given its total variation, then the method down weights mutations in this gene, as it is unlikely to be functionally significant, and visa-versa. Applying this method across the genome identifies c. 4,000 genes that are intolerant to standing functional variation and are therefore more likely to carry mutations that cause disease.

A relatively small sequence analysis of the exomes of 264 epileptic encapholohy probands, and their parents, confirmed 329 de novo mutations. A likelihood analysis showed a significant excess of these de novo mutations in the c. 4,000 intolerant genes. Some of the genes with multiple de novo mutations were known to cause epileptic encapholohies. Others are novel, potentially providing new mechanistic insights.

This small sequencing study, found that more than 10% of patients could be genetically explained. These and other similar analyses suggest that for some complex human diseases

that are strongly genetic we can imagine a future where most patients presenting with the disease will have an identified causal/contributing mutation. This will be transformative. Trials will then need to be stratified by genes / pathways that are dysregulated by the causal mutations. It is also likely that cellular screening programmes can be developed that will prove useful both for optimizing care for individual patients amongst available treatments, and for developing entirely new therapeutic directions.

3. Opportunities and Challenges in Undertaking Stratified Medicine Research

The aim of this session was to reflect, at a more granular level, on how best to design and undertake stratified medicine research and how this might be implemented into practice e.g. trials. For this session speakers were asked to present cross cutting themes, drawing on their own research.

Professor John Isaacs (Newcastle University), Co-Principal Investigator to the MRC/ABPI Rheumatoid Arthritis Consortium, presented a view of the challenges posed in identifying predictive markers of response.

In order to identify biomarkers of response, you need clear measures of response. While objective measures are better than subjective ones, key measures in rheumatoid arthritis, such as pain, are subjective. The choice of outcome measures also varies depending on their use. NICE looks at quality of life outcomes. While, for patients, patient reported outcomes are critical.

In addition to selecting appropriate response criteria, you need to select your study population. If this population is too homogenous then you may not have sufficient diversity for the signal (differential response to drug) to emerge. Conversely too much diversity and the signal may get drowned out.

Once you have selected outcome measures and a study population you still need to consider when to measure outcomes and when to collect samples for biobanking. For the former, an understanding of the drugs pharmacokinetics and immunogenicity (primary vs secondary) are important. While for the latter, you need to consider when best to set the baseline for stratification and at what points downstream of this you will make additional collections. These collection points, which may need to take into account time of day, fasting etc, should be harmonized through the use of SOPs and central storage facilities.

Stratified medicine is a team game. You need the input of multiple stakeholders from the planning stage. These include patients (end users as well as charities), industrial partners, biostatisticians, trial designers, clinicians and laboratory scientists. Industry partnership is critical for access to new therapies but also for good pharmacokinetic and pharmacodynamic measures. Industry can also be helpful in co-ordinating efforts, not necessarily a strength of academics. The involvement of an experienced project manager is also essential in this regard and plans need to factor in sufficient time for securing contracts and agreements. First build the team then face the challenges.

In conclusion, stratified medicine offers a great potential to improve patient outcomes. However, robust stratified medicine studies pose significant challenges in multiple domains. Even where stratification is clear, a stepwise approach may be required, which includes the definition of patient groups, robust outcomes and then trial design. An 'informed' design should lead to stratifiers as well as novel information about disease mechanisms.

Dr Ellie Barnes (University of Oxford), Principal Investigator of the MRC STOP-HCV Consortium) described the advances that have been made in stratifying HCV response and the challenges that remain.

HCV provides a great example of the power of pharmacogenetics. GWAS studies described by Professor Goldstein identified a marker for response to interferon that has been used to direct therapy. However, we know that there are many other factors involved including host factors

such as the extent of fibrosis, age, the older being less likely to respond, and gender, with men much less likely to respond.

Unlike in non-pathogenic diseases, in HCV we know the cause. In the 1980s everyone got interferon and only c. 10% were cured. Next interferon plus ribavirin was used. Patients with genotype-1 (gt-1) infections had a c. 50% response rate. However for gt-3 patients, the response rate remained at c. 10%.

There are 13 new HCV drugs in the pipeline, most of which are only effective against gt-1, with only one having potential against gt-3, which, along with gt-1, is the most prevalent form in the UK. Most work has been done on gt-1, in part as it is the most prevalent form in the United States, and the new protease inhibitors are aimed at this genotype.

Optimally we would like to compare the new drugs against each other. However as each is owned by a different company, we may need to wait until post licensing. In our first study we will be tracking response in the gt-3 population in collaboration with an industrial partner. The consortium will be sent samples from each participant. This is the first time we have worked with industry in this way.

Professor Max Parmar (MRC Clinical Trials Unit) discussed biomarker search strategies and new clinical trial designs able to assess multiple drugs and stratification strategies simultaneously, thereby optimising outcomes.

Many response biomarkers have been identified retrospectively rather than prospectively. If we insist that markers be identified prospectively, we risk getting many negative results on validation. In validation but not exploration, randomization with control groups not receiving treatment has been key.

Many new treatments are found to be effective in only c. 30-40% of patients in Phase III trials, perhaps because we are drowning out a signal from an unknown sub-group of patients. If we were able to identify this sub-group, we could increase the positivity rate. However, if all we do is pull out the poor responders, we will not increase benefit to the whole population. Although biomarkers are promising, what we need are new effective treatments.

We need to design future trials more strategically. We need to include all patients recruited, and assess many treatments and many biomarkers. Separate biomarker-based trials are inefficient, as either many screened patients are not eligible or both marker selected and unselected patients are included. Trials need to be able to adapt to information as it emerges both within and without the trial. We should concentrate on new treatments first and new biomarkers secondarily. You cannot wait for a fully validated biomarker before developing the treatment or visa-versa. You need to have a way to do this in combination.

Professor Parmar then presented FOCUS4 as an example of a more efficient and adaptable trial design. This trial, which is focused on patients with inoperable metastatic CRC, is a programme of multiple, parallel, molecularly stratified randomised comparisons. It will encompass all biomarker defined/enriched cohorts and is adaptable to new emerging biomarkers. It tests treatment first and then whether activity is specific to the molecular sub-group. Biomarkers do not have to be completely characterised or fully validated upfront. The trial design provides an efficient means of ascertaining specificity of any positive results in relation to the biomarker selection used.

Dr Ian Dix (AstraZeneca) discussed the challenges posed by managing and analysing the diversity and volume of data generated in stratified medicine studies.

Projects underestimate the efforts required in data management. The challenge is mainly information technology service rather than information technology research. However, support for services does not fit well with research funding models.

An absence of standards leads to poor interoperability and results in islands of data, making

discoverability and mining hard. A national strategy could help but appears absent. You do not want to standardise everything. Some aspects it would be beneficial to standardise but for others you want to allow innovation. Data management and sample tracking are areas for standardization. Data capture and analytics are areas where you want more flexibility.

There are existing solutions that we might build on. For example

- UBIOPRED has a system up and running that is able to tell you where a sample is, what shipments are coming your way, etc.
- The TRANSMART platform, which is based on the i2b2 platform from Boston, can pool data and then allows you to do analytics on top.

The adoption of a common platform could aid data sharing and archiving and help drive entrepreneurial business models producing new plug-in analytical tools and delivering support services.

Currently there are a number of initiatives addressing aspects of the data integration challenge but are these appropriately linked? In addition, do we have the right models and metrics to fund service functions compared to research activities? In the pharmaceutical industry there are support functions (IT function, discovery function, etc), which provide services to research projects. Is a similar model appropriate for the stratified medicine consortia?

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