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**Working together to deliver Stratified Medicine research effectively**

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**Abstract**

Stratified medicine has become an extremely important area of medical research across all clinical specialties, with far reaching impact in health economic, societal, political and industrial spheres. Despite recently formulated policy and research programmes across many countries, major challenges for delivering stratified medicine studies persist. Across the globe, national and specialty specific clinical research infrastructures have been set up over the last couple of decades to facilitate high quality clinical research. This paper examines the critical contribution clinical research networks and infrastructures can make to the successful delivery of national (and international) initiatives in the field of stratified medicine. Importantly, it examines the position of clinical research in stratified medicine at a time when pressures on the clinical and social services are mounting in many countries.

**Keywords (3 - 10 words)**

Stratified Medicine

Personalised Medicine

Precision Medicine

Clinical Research

Research Networks

**Background**

Stratified medicine, providing the right patient with the right drug at the right dose at the right time, is widely recognised to be of huge potential global benefit.1,2,3 Also termed personalised or precision medicine,3,4 stratification is undertaken to identify and analyse patients to better direct therapy and to gain a deeper understanding of the differing mechanisms of disease and treatment responses. Stratified medicine has become an extremely important area of medical research across all clinical specialties, with far reaching impact in health economic, societal, political and industrial spheres.5 In the treatment of cancer, it is already being implemented based on molecular changes in the somatic genome and is leading to a step-change in care, not only in the use of targeted drugs but also in the use of the same drugs across different cancers with the same mutations.6 For example the *BRAF* mutation, first identified in malignant melanoma, has also been identified in other malignancies, for instance hairy cell leukemia, and has led to the use of vemurafenib for these two apparently disparate malignant conditions.7

Healthcare providers in many countries including United Kingdom (UK), USA, Canada, Australia, China and India have proactively formulated policy and research programmes in this field with substantial investments.8–12 The precision medicine initiative (PMI), launched by former US President Obama in his State of the Union address in January 2015, with a budget of $215 million, gave significant momentum to these efforts.2,13 The European Union-funded 'PerMed' project, including representatives from all EU Member States, countries associated to the EU research framework programme and other stakeholders, is developing a European strategy framework for personalised medicine.14

Across EU Member States, many key initiatives have been launched to support stratified medicine research and implementation.15,16 In the UK, the National Institute for Health Research (NIHR), the Medical Research Council (MRC), the Academy of Medical Sciences, Innovate UK and the Association of British Pharmaceutical Industries (ABPI), NHS England and others, have led a series of such initiatives, including workshops, conferences and reports on stratified medicine. Many of these outline key recommendations and highlight future programmes that must address the urgent need to develop robust new approaches through to implementation of stratified medicine at scale in clinical practice.17-20

In parallel, national and specialty-specific clinical research networks have been set up worldwide to facilitate the delivery of clinical trials .21-25 Established networks streamline and coordinate research activities providing efficiency for sponsors of trials,26 benefit to investigators27 and availing patients and the public opportunities to participate in clinical research.28,29

This paper explores major challenges for delivering stratified medicine studies. In bringing together the perspectives and challenges from the many key stakeholders involved in this process, it demonstrates the critical contribution clinical research networks make to the successful delivery of national (and international) initiatives in the field. Importantly, it examines the position of clinical research in stratified medicine at a time when pressures on clinical and social services are mounting in many countries.

**Stakeholders in stratified medicine**

***The Patient and Researcher***

At the heart of successfully delivering stratified medicine must be the patient. Without recognising and integrating their needs and perspectives, from study design to delivery and implementation of the study’s findings, stratified medicine studies will remain very challenging and at times impossible to achieve. Excellent examples where patients and public have been an integral part of development through to adoption of new medical innovations exist.29 For instance, a survey of patient involvement in randomised controlled trials and other studies run through the UK Medical Research Council Clinical Trials Unit suggests that consumer involvement had multiple benefits including on the design and quality of the studies, on recruitment, and on dissemination of findings.30 Major improvements have been made in effective engagement and partnership with the patients and the wider public in the design and delivery of clinical studies/trials at organisational as well as an individual trial level.31 However, internationally this role remains variable and a structured, robust, appropriate and consistent approach is still required.3,32-34

Within stratified medicine research, this issue is further compounded by all too frequent inconsistencies in nomenclature and lack or misunderstanding of the concepts underpinning the field. Important partnerships and initiatives have started to address how individual patients and the public in general, understand and respond to the concept of stratified medicine.35 Having a clear, consistent definition remains a basic challenge for stratified medicine.35

Interpretation of terminology used may also conjure negative perceptions of equality and impact on participation. The challenge for stratified medicine studies is that often many patients need to be screened to identify a small proportion of people with the relevant biomarkers. For example, *ALK* mutations in lung cancer are only present in 3% of patients, which means that many people approached were not suitable to participate in the ALK inhibitor trial.36 This can easily present a barrier to involvement by patients who may worry that they may have a form of a disease where there is no treatment option, thereby creating therapeutic orphans, something which needs to be considered in all disease areas. For these reasons, novel ways are being developed to overcome this; for example, novel trial designs such as umbrella trials, multi-arm, multi-biomarker trials where the drug choice is dependent on the biomarker are now becoming more common.37 Any study design should take into account the effect of the treatment to those who do not have any of the specific biomarkers, which provides a more inclusive research design for the patient.38

In pharmacogenomic studies, sample size is dependent on the population frequency of the allele of interest, and its effect size. This can lead to problems of identifying adequate numbers of patients exposed to the drug of interest – for example, in a prospective cohort study of carbamazepine patients, 4855 subjects were recruited to identify 372 who carried the risk *HLA-B\*15:02* allele.39 The requirement of large sample sizes for rare phenotypes, for example for serious adverse drug reactions, can be problematical for the researcher in trying to identify a large enough sample size of accurately phenotyped patients. Where pharmacogenomic variants can determine dose requirement, a validated algorithm may determine the success or otherwise of a trial, and small differences in the algorithm can lead to marked changes in trial outcomes, as witnessed with warfarin.40

Open debate about key issues, providing relevant and accurate information and clarifying patients’ concerns is key to progress here. Advancing public and patient engagement initiatives through specialty specific organisations can help provide access to patients and communicate research opportunities and findings.41 Assimilation with wider patient and public engagement initiatives has already commenced to unify work across regulatory, clinical and research settings which is important for stratified medicine.42-44

Development and delivery of stratified medicine studies involves a very wide range of disciplines and perspectives, irrespective of whether the study is led from within the life sciences industry or academia. The research workforce no longer constitutes only the traditional clinician investigators, clinical nurses and data collection and entry staff who work across clinical trials within clinical settings.28,45 Stratified medicine studies take place in a wide variety of clinical environments, within and outwith the hospital inpatient or outpatient context. Studies may take place in patients’ homes (for example using digital technologies), in primary care, or in specific translational and/or experimental research centres or units. For industry sponsored studies, although the funding and design of the trial may come from the company, successful delivery of the study will still depend on staff and facilities within the healthcare setting. In the UK, these include for example NIHR Biomedical Research Centres, Clinical Research Facilities and a wide range of other clinical research infrastructure resources.46 Research training and education, especially supporting effective stratified medicine studies, does not currently address this wider community of professionals. These span multiple sectors within and outwith hospitals, including biostatisticians, basic scientists, analysts and data-miners who may have limited experience within the clinical research environment. 47

Identifying the workforce involved requires careful mapping of the activity of these studies/trials to the clinical context of delivery. It needs a careful understanding of the breadth and the scope of the infrastructures involved in the delivery of stratified medicine research, which is often not sub-specialty specific, and which spans diagnostics through to treatment intervention and involves multiple disciplines in its approach.48 Clinical and research staff training needs to include supporting patients to make sound treatment decisions in this field.37 There is a need to develop cross-disciplinary training, for example clinicians trained in informatics; this is going to be challenge given that there is already a lack of appropriately-trained staff in fields such as bioinformatics. 49,50

Clinical research networks, including the NIHR Clinical Research Network in the UK, along with other research delivery infrastructures, are uniquely placed through their specific strategic focus on training and education, to take a lead role in assisting to identify and map the expertise and training requirements to support effective delivery of stratified medicine across a wide range of clinical environments.51 Together, they can impact significantly on raising awareness and leading programmes that deliver a priority focus for appropriate training with continued engagement activities to support the needs and developments of these key components of the stratified medicine workforce.52

***The Science***

Whilst randomised clinical trials (RCTs) remain the gold standard of evidence for the benefit of new therapeutics, standard trial designs may not always be possible, appropriate or efficient in the development of new drugs, repurposing of old drugs, or in the development of biomarkers for off-patent drugs. This applies to non-pharmacological interventions as well including those using advances in digital technologies.53-55

Trials investigating one biomarker/drug pairing at a time, are very inefficient,45 particularly when the biomarker has a low prevalence in the population with disease. Umbrella trial adaptive designs represent an opportunity to undertake multi-arm, multi-biomarker trials, but there are some statistical challenges. These trial designs offer adaptability to evolving knowledge about the biomarker(s) and drug(s) being tested.

The FOCUS4 trial, funded by Cancer Research UK and supported by the NIHR Clinical Research Network was designed to overcome some of these challenges.38 It is an integrated trial programme of parallel, molecularly stratified, and randomised comparisons of maintenance therapies for patients with advanced or metastatic colorectal cancer after receiving 1st-line chemotherapy; it includes a platform for recruiting almost all potential patients with colorectal cancer in a biomarker-driven trial, regardless of biomarker status. It has an “umbrella design” - a stratified trial design with nested, virtually separate, parallel RCTs for biomarker-defined subgroups of patients, each with its own appropriate control. Each of these, a separate randomised phase II/III trial could stop early for lack of benefit or continue to its final stages.

Clinical research networks offer a unique breadth and reach for recruiting patients either nationally or across disease-specific contexts internationally. Patient-centric approaches to trial designs are important, for example to deliver trials close to where the patient is in the community,56 through digital connectivity,57 through local hubs that have research workforces that cover regional areas rather than the traditional settings of clinics and wards,58 as well as recruiting to rare diseases (nationally and internationally) effectively and in a timely manner59.

***The Infrastructure***

*Regulations*

Stratified medicine has tremendous potential to utilise trial designs in an innovative and iterative way to benefit patients. Clinical research infrastructure and procedures may not currently be optimised to deliver these benefits to patients in similar innovative style.60,61 National regulatory procedures are generally designed for a single drug/intervention at multiple sites. In response to the progress and importance of a streamlined approach to overcoming the many barriers to safe and effective regulation of clinical research, regulatory bodies are now working to consider novel approaches to evaluation of stratified medicine studies. For example, the UK’s Health Research Authority has an explicit ambition “...to protect and promote the interests of patients and the public in health research, and to streamline the regulation of research”.62 This may include accepting different levels of evidence to give approval for medicines, diagnostics or other types of interventions, including algorithms developed through artificial intelligence techniques. A proportionate approach which protects public health while at the same time ensuring that regulation does not stifle innovation will be crucial for the future, and will require wide discussion amongst multiple stakeholders. A good example of such a wider discussion, and one which is of particular importance to stratified medicine is the Wellcome Trust’s setting up of an independent patient data taskforce, which aims to “support better conversations about the uses of health information, and to provide objective evidence about how and why patient data can be used for care and research”.63

*Data and digital platforms*

Many emerging sources of ‘big data’ have created an opportunity to transform medical science. There are research methodologies and tools being developed on managing, analysing, visualising, and extracting information from large, diverse, complex, longitudinal, and/or distributed biological, biomedical and healthy data sets to support stratified medicine.64  The existing systems, however, require effective mechanisms for storing and linking data.65 This requires standardisation to be improved for the collection, storage, and sharing of samples (across Europe).66 Procedures for informed consent, future use of samples, potential of sample withdrawal and other related challenges associated with stratified medicine studies need to be fully harmonised.67 Compatibility of legal and regulatory frameworks and consistency in ethical committee standards that oversee these processes would also enable biobank networking initiatives and would facilitate drug efficacy and safety studies across different populations.66

In addition to inter-institutional sharing, data collected during clinical trials and through patient care pathways offers an outstanding, unique and more complete understanding of individual health that would impact significantly on delivering stratified medicine studies.68 This could be achieved through efforts to integrate these different layers of data, including molecular ‘omics datasets, clinical phenotype data, knowledge of the environment that a subject has been exposed to and citizen-contributed information.65,69 Investment is required in the fields of bioinformatics, biomathematics, and biostatistics to develop translational analyses of ‘omics’ data.69

One of the most active areas of research which is having an increasing impact on stratified medicine is the development of machine learning techniques for the analysis of large genomics and other -omics data sets. Recent progress is likely to reflect the increasing availability of large well-curated data sets as well as the development of novel algorithms. A recent review by Librecht and Noble, noted the value of a range of machine learning applications for the analysis of genome sequencing data sets, including sequence annotation and epigenetic data.70

Exploiting established digital platforms for identifying potential patients, trial set-up and design; empowering patients to be able themselves to be aware of a potential trial,71 self-consenting and enabling them to send in appropriate samples to a named investigator at a clinic would be a significant step forward. Other organisations have made that leap into mobilising public interest and activity through platforms such as the Apple research kit.72

*Cross-border working*

Research workforces that can transcend organisational borders to recruit effectively and efficiently are critical to overcome the challenges of stratification arms and the paucity of patients that fit criteria of each arm, including the challenge of the large numbers of patients that require screening to recruit a sufficient number to satisfy inclusion/exclusion criteria. Amongst factors that hinder cross-border working include lack of standardisation of terminology, lack of standardisation of data capture forms, requirements of metrics and reporting of individual organisations and networks.

Frequently there is regional and national variability in assessing the feasibility or more specifically evaluating the number of patients that will be eligible for a certain study at sites. This is of course not unique to stratified medicine studies, but affects all studies due to differences in staff expertise and experience, and process and time taken to make this assessment across different sites and regions. The feasibility of stratified medicine studies may be more complicated requiring more time and effort because of the need to more deeply phenotype patients, or ascertain genotype, to determine suitability for a particular arm. Better and more accurate ways of assessing feasibility are needed, and could for example include feasibility stages built into the trial design.

For effective research delivery, the fundamental point to address is how well research is embedded into healthcare provision and established patient pathways.73 The challenges associated with undertaking clinical trials in an environment which is naturally geared for clinical treatment delivery have been extensively catalogued by various stakeholders.74-76 Discernible progress has been made in the UK in the National Health Service, facilitated by dedicated research delivery networks, and the 100,000 Genome project is providing valuable insights into how genomics can be embedded in clinical services.18 However, the specific complexities of stratified medicine research, which may not map neatly onto to a specific clinical (disease-focused) treatment pathway, pose significant challenges for recruitment which will need adaptation into how clinical research delivery networks work. 77-79

Multi-stakeholder collaboration to accelerate the development and adoption of stratified medicine has been highlighted and recommended across many important reports.80-83It is imperative that initiatives build on existing work undertaken and contribute to added value for all stakeholders involved.

**Conclusion**

Despite stratified medicine being a major political and health-related policy for clinical research nationally and internationally over the last 5 years with significant associated investment from governments and industry, considerable challenges exist to undertaking and above all delivering stratified medicine research programmes. Addressing and agreeing a roadmap to tackle the key priority areas identified will enable the right support and training to be delivered to the workforce involved in undertaking stratified medicine studies.

Multi-stakeholder collaboration to accelerate the development and adoption of stratified medicine, highlighted and recommended across many important reports,has led to the creation of national and international consortia, including those present in the UK. These represent important drivers for the development of stratified medicine, but will continue to struggle to deliver, unless identification, phenotyping and recruitment of patients is optimised. These challenges are part of all forms of clinical research, but as we have highlighted, there are some key issues for stratified medicine, which make these studies even more difficult to deliver. It is also important to highlight that these challenges are not unique to studies which are academic in origin, but also affect industry-sponsored studies. It is important that these challenges are addressed effectively and promptly by clinical research networks who are well placed to support the delivery of these studies. Effective partnership working at all levels, built upon experience and the availability of highly trained clinical research delivery staff, will be important to ensure that we can develop the evidence base necessary to implement novel treatments and clinical pathways to improve outcomes for patients, and aid industry as they transition into new models of drug development which focus on targeted or stratified medicines, aimed at sub-populations with a particular disease, rather than the conventional one-drug-fits-all model.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and material**

Not applicable

**Competing interests**

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**Authors’ contributions**

SA collated the findings of the workshop into a report which formed the basis of the article, and participated in the writing of the article. VP, NL, SL, MP and MB participated in the design and organisation of the workshop and in the writing of the article. JB, DH, SL and LO acted as rapporteurs of the discussions at the workshop and contributed to the report upon which this article is based.

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