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Working together to deliver Stratified Medicine research effectively

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Short Title: Delivering stratified medicine research

Abstract

Introduction or background

Stratified medicine is an important area of research across all clinical specialties, with far reaching impact in many spheres. Despite recently formulated global policy and research programmes, major challenges for delivering stratified medicine studies persist. Across the globe, clinical research infrastructures have been set up to facilitate high quality clinical research.

Sources of data

This article reviews the literature and summarises views collated from a workshop held by the UK Pharmacogenetics and Stratified Medicine Network and the NIHR Clinical Research Network in November 2016.

Areas of agreement

Stratified medicine is an important area of clinical research and health policy, benefitting from substantial international, cross-sector investment and has the potential to transform patient care. However there are significant challenges to the delivery of stratified medicine studies.

Areas of controversy

Complex methodology and lack of consistency of definition and agreement on key approaches to the design, regulation and delivery of research contribute to these challenges and would benefit from greater focus.

Growing points

Effective partnership and development of consistent approaches to the key factors relating to stratified medicine research is required to help overcome these challenges.

Areas timely for developing research

This paper examines the critical contribution clinical research networks can make to the 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.

Keywords (3 - 10 words)

Stratified Medicine, Personalised Medicine, Precision Medicine, Clinical 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 better direct therapy to gain a deeper understanding of the differing mechanisms of disease and treatment responses. Stratified medicine has become an 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 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, 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 challenges for delivering stratified medicine studies. Reviewing 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

Failure to recognise and integrate the needs of patients in research, from study design and delivery, to implementation of the study's findings, renders stratified medicine studies 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 studies run through the MRC Clinical Trials Unit suggests that consumer involvement had multiple benefits to the design and quality of the studies, the recruitment, and dissemination of findings.³⁰ Major improvements have been made in effective engagement and partnership with 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, appropriate and consistent approach is required.^{3,32-34}

Within stratified medicine research, this issue is further compounded by all too frequent inconsistencies in nomenclature and 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 these 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 have a form of 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, umbrella trials, multi-arm, multi-biomarker trials where the drug choice is dependent on the biomarker are 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 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 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 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, in primary care, or in specific translational and/or experimental research units. For industry sponsored studies, although the funding and design of the trial may come from the company, delivery of the study will still depend on staff and facilities within the healthcare setting. In the UK, these include NIHR Biomedical Research Centres, Clinical Research Facilities and a wide range of other clinical research infrastructure resources.⁴⁶ Research training and education, 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 which is a challenge given the 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 focus on training and education, to take a lead role 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

NIHR Clinical Network Support for the ASTRAL 3 Trial⁵³

The ASTRAL 3 trial was a multicentre international trial exploring treatment options for patients with a particular genotype of hepatitis C virus (HCV). Patients with HCV genotype 3, one of the most common types in the UK, were randomised to receive either a combination of sofosbuvir and velpatasvir for 12 weeks or 24 weeks of sofosbuvir and ribavirin (standard treatment). Randomisation was stratified according to whether or not cirrhosis was present at screening, and previous treatment status. A total of 277 patients were recruited to the treatment arm, and 275 to the control arm. The study found the new treatment regimen to be more effective than previous regimens and the results have been incorporated into treatment guidelines for the condition.

The NIHR Clinical Research Network supported the delivery of this commercially-sponsored study by facilitating study set up at the 10 UK sites, provision of funded research nurse time, and contributed to the screening and recruitment of patients.

The Science

Whilst randomised clinical trials (RCTs) remain the gold standard of evidence for the benefit of new therapeutics, standard trial designs may not 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.⁵⁴⁻⁵⁶

Trials investigating one biomarker/drug pairing at a time, are 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 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,⁵⁷ through digital connectivity,⁵⁸ through local hubs that have research workforces that cover regional areas rather than the traditional settings of clinics and wards,⁵⁹ as well as recruiting to rare diseases (nationally and internationally) effectively and in a timely manner⁶⁰.

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.^{61,62} 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 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”.⁶³ This may include accepting different levels of evidence to give approval for medicines, diagnostics or other types of interventions. A proportionate approach which protects public health whilst ensuring that regulation does not stifle innovation is crucial, and requires wide discussion amongst multiple stakeholders. A good example of this 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”.⁶⁴

Data and digital platforms

Many emerging sources of ‘big data’ have created an opportunity to transform medical science. Research methodologies and tools are being developed to manage, analyse, visualise, and extract information from large, diverse, complex, longitudinal, and/or distributed biological, biomedical and healthy data sets to support stratified medicine.⁶⁵ Existing systems, however, require effective mechanisms for storing and linking data.⁶⁶ This requires improved standardisation for the collection, storage, and sharing of samples.⁶⁷ Procedures for informed consent, future use of samples, potential of sample withdrawal and other related challenges associated with stratified medicine studies need to be harmonised.⁶⁸ 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.⁶⁷

In addition to inter-institutional sharing, data collected during clinical trials and through patient care pathways offers a unique and more complete understanding of individual health that would impact significantly on delivering stratified medicine studies.⁶⁹ This could be achieved through efforts to integrate different layers of data, including molecular ‘omics datasets, clinical phenotype data, knowledge of the environment that a person has been exposed to and citizen-contributed information.^{66,70} Investment is required in the fields of bioinformatics, biomathematics, and biostatistics to develop translational analyses of ‘omics’ data (see Table 1).⁷⁰

Table 1. Glossary of related terms

‘Omics’	Areas of study within the field of biology generally associated with large amounts of data, for example genomics, proteomics and metabolomics ⁷¹
Bioinformatics	The application of methodologies and software tools to the understanding of biological data ⁷²
Biomathematics	The application of mathematical tools and techniques, and theoretical analysis to investigate principles relating to living organisms ⁷³
Biostatistics	The application of statistical methods to the design, analysis and interpretation of biological experiments ⁷⁴

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 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 review by Librecht and Noble, noted the value of machine learning applications for analysis of genome sequencing data sets, including sequence annotation and epigenetic data.⁷⁵

Exploiting digital platforms for identifying potential patients, trial set-up and design; empowering patients to be able themselves to be aware of a potential trial,⁷⁶ 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.⁷⁷

Cross-border working

Research workforces that 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 and 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. Feasibility of stratified medicine studies may be more complicated and require more time and effort because of the need to 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.⁷⁸ 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.⁷⁹⁻⁸¹ Discernible progress has been made in the UK 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 a specific clinical (disease-focused) treatment pathway, pose significant challenges for recruitment which will need adaptation into how clinical research delivery networks work.⁸²⁻⁸⁴

Multi-stakeholder collaboration to accelerate the development and adoption of stratified medicine has been highlighted and recommended across many important reports.⁸⁵⁻⁸⁸ It is imperative that initiatives build on existing work undertaken and contribute to added value for all stakeholders involved.

Conclusion

Despite stratified medicine being part of political and health-related policy nationally and internationally over the last 5 years with significant investment from governments and industry, considerable challenges exist to undertaking a 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 that are well placed to support the delivery of these studies. Effective partnership 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.

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