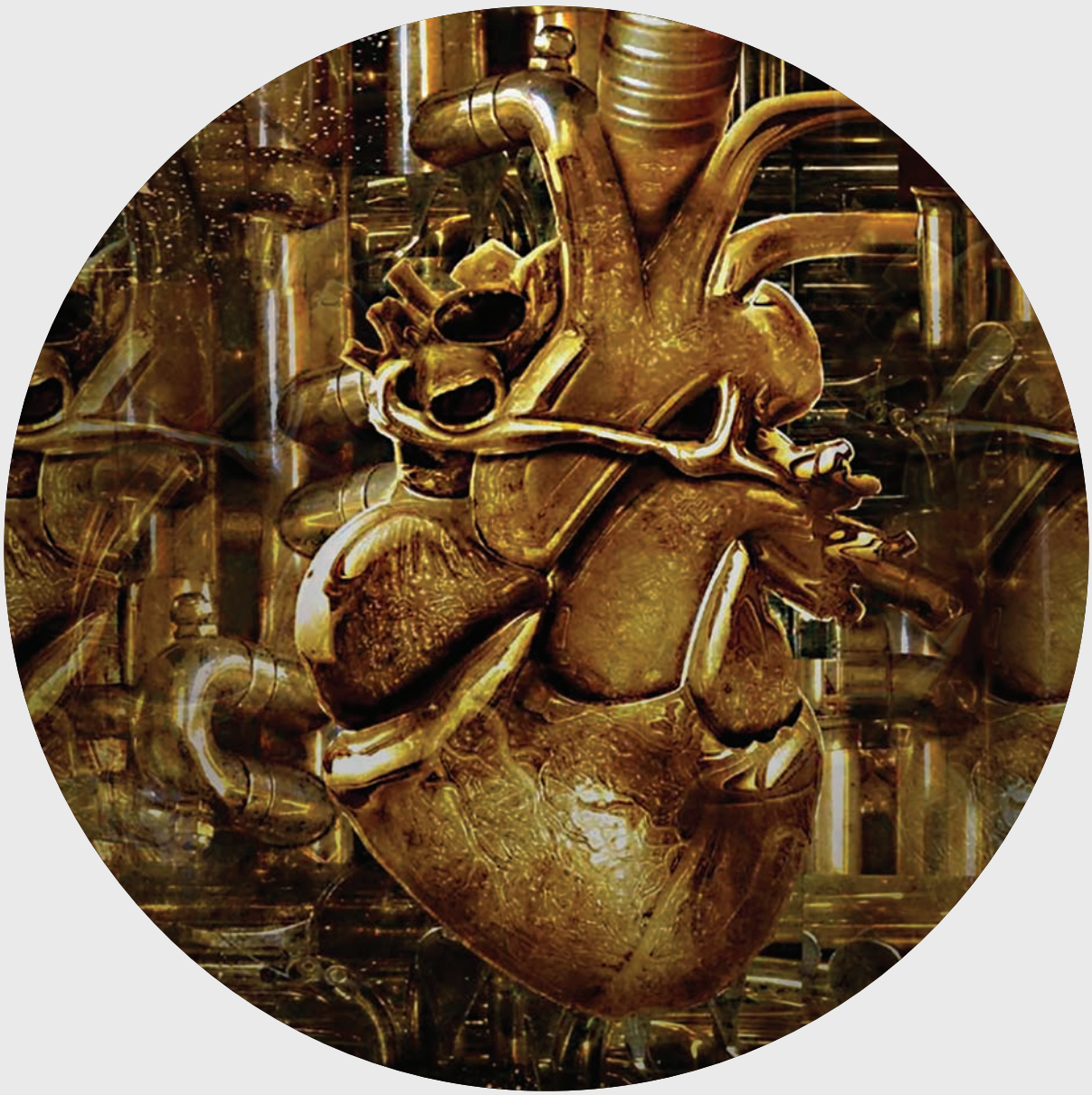
Medical Engineering Initiative

Opportunities and Challenges

Advancing and Translating Knowledge and Technology



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MEDICAL ENGINEERING INITIATIVE

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Opportunities and Challenges

Advancing and Translating Knowledge and Technology

A report of the discussions at the MEI Strategic Workshop September 2015

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INTRODUCTION

The purpose of this workshop, held as part of the annual Medical Engineering Initiative (MEI) meeting, was to gather a diverse group of over 30 different stakeholders to discuss the opportunities and challenges of advancing knowledge and technology in the field of medical engineering and technology. Specifically, the workshop discussions addressed:

- the opportunities for innovation in the medical engineering technology landscape, as seen from a user perspective, as well as from an academic research perspective
- the challenges faced in translating applied research to deliver improved products and services and patient and economic benefits
- the creation and advancement of knowledge in related areas of science and engineering, which may contribute to medical engineering innovation and translation and opportunities arising from collaboration across different areas of research
- the future opportunities and directions for medical engineering research and innovation.

The workshop recognised that opportunities and challenges in translation vary across the different parts of the medical technology sector and for different types of technologies. To this end the workshop was structured in five themes, each addressing a different market segment, as reflected in this report. Each theme was discussed by a different group of stakeholders. The five discussion groups were based on the following thematic areas:

1. Physical devices, implants and biomaterials
2. Regenerative devices and therapies
3. Surgical technologies and robotics
4. Imaging
5. E-health, sensors and diagnostics.

The workshop built upon the recent strategy statement from the EPSRC Healthcare theme, which identified a number of research challenges and areas. Specifically, this MEI workshop chose to focus on the medical engineering landscape and the opportunities and challenges faced in the advancement of knowledge and technology and the translation of research. Over 30 people representing industry, the health service, regulators, investors, funders and academia participated in the workshop discussions.

Each thematic area group had the opportunity to address some of the following questions:

1. Opportunities from the user perspective - the pull

(a) What are the key unmet clinical, industry, market, regulatory, user needs and the opportunities for business and service improvement from an industry, clinician and patient perspective?
(b) How might these be addressed through, and what opportunities do these create, for development and translation of new technologies and improvement of existing technologies?

2. Challenges faced in translation - the barriers to translation

(a) What are the key gaps in knowledge and challenges faced in applied research that are acting as barriers to translation?
(b) What are the important research questions that need to be addressed and the areas of knowledge and technology that need to be addressed?
(c) Are there any systematic barriers to advancement of knowledge and translation of technology in this area and how might hey be addressed?

3. Opportunities created by research base push

(a) What are opportunities arising from major breakthroughs in science and technology in the last decade?
(b) What are the opportunities arising from research and advancement of knowledge and technologies in other areas (8 great technologies and other industry sectors)?
(c) What are the opportunities for research and translation that are linked to, or associated with, the other four themes?
(d) What are the future opportunities and directions for medical engineering research and innovation?

This report captures the outcome of the discussions in the five separate thematic groups. In order to capture the authenticity of the discussion in each group and how each group chose to address the questions outlined above, the outcome of the discussion in each group has not been edited into a standard format. The intent of this report is to capture and provide insight into the views of the many different stakeholders involved in, or with an interest in, early stage translation of research in the field of medical engineering in each of the technology/market areas. The short period of time that the stakeholders were gathered together did not allow time for further synthesis or reflection on the discussions, nor did it allow significant interaction between the thematic groups. In this context, this report should be taken as the starting point for further discussion on translation of medical engineering technology, which may be addressed through the thematic approach defined in this workshop.

OVERVIEW

The advancement of knowledge and technology leading towards and supporting successful innovation and development of new products and technologies to deliver benefits to patients and the economy is a core part of the missions of both the EPSRC and the Wellcome Trust. This complements discovery science and creation of new knowledge which is also a key part of their missions as sponsors and funders of research. Engineering (the application of science with a defined purpose), and in particular medical engineering, has an increasingly important role to play in the advancement of knowledge and in technology innovation in medicine and health.

It is now widely recognised that many scientific discoveries today come from collaborative work which involves many academic disciplines. This is equally important in medical engineering research. Furthermore, when considering the advancement of knowledge and technology innovation (beyond discovery-led research at Technology Readiness Levels (TRL) 1 & 2), which can lead to successful translation and support the development of new products or services in the future, it is necessary to engage and involve a much wider set of stakeholders. These stakeholders include industry, healthcare providers, clinicians, patients, regulators, policy makers, funders and sponsors, as well as academic researchers. In challenge-led research (TRL 2 & 3) and in early stage advancement and translation of knowledge technology (TRL 3 to 5), the definition of the direction of travel, the target clinical or economic need, the existing market and current practice, the translation pathway, the regulatory environment and the nature of the added value proposition are all important considerations in setting the research priorities and questions. The research priorities and questions cannot be defined by academics alone and the importance of the pathway and environment for translation and views of the translation stakeholders was clearly evident in the discussions and the views recorded in this workshop.

There are many different translation pathways and regulatory routes for different types of medical engineering technologies. Indeed, the role and timing of pre-clinical evaluations, evaluations in animals, the point at which a clinical study is undertaken, the point of entry and time to market and the product lifecycle vary considerably

for different technologies and products. This leads to considerable diversity in the definitions of the challenges and opportunities in the different thematic areas and market sub-sectors considered in this workshop. This differentiation in the translation pathways and the routes to commercial development and market adoption for the different groups of technologies needs to be considered when establishing the priorities for challenge-led research and advancement of knowledge and technology.

Some common issues were identified across the thematic groups, some of which aligned to topics identified in the EPSRC Healthcare Technologies Grand Challenge statements, including the need for stratification of the population and the patient needs, improved diagnostics and characterisation, increased levels of precision in design and delivery of interventions, the need for greater simulation capability, the ability to predict function and outcome in highly variable populations, consideration of both regulation and reimbursement pathways and the need to be able to generate evidence of effectiveness through improved clinical endpoints. These were interpreted and contextualised differently in the different thematic areas and discussion groups in the descriptions that follow.

John Fisher

PHYSICAL DEVICES, IMPLANTS AND BIOMATERIALS

There is a need for improved stratification to better match patient and intervention, and earlier diagnosis to enable early-stage treatment

Theme lead:
Ruth Wilcox, Professor of Biomedical Engineering, University of Leeds

Attendees:

- John Wilkinson, Director of Devices, Medicines & Healthcare Products Regulatory Agency (MHRA)
- Ian Revie, Business Manager – Knees, Invibio Ltd
- Graham Isaac, Distinguished Engineering Fellow, DePuy Synthes
- Anthony Bull, Head of Department of Bioengineering, Imperial College London
- Liam Grover, Professor of Biomaterials Sciences, University of Birmingham
- Nick Eldred, Director, Simulation Solutions Ltd
- Matt Chapman, Manager – Medical Technologies, The Knowledge Transfer Network
- Helen Hurman, Head of Research Operations, Arthritis Research UK.

Summary of discussion

Due to the expertise and area of interest of the participants in the group, the focus was almost entirely on musculoskeletal (MSK) interventions. The umbrella of 'physical devices, implants and materials' covers both well-established clinical techniques and emerging areas and the major unmet needs that were identified reflect these different levels of maturity. At the most established end of the spectrum, there is a need for more robust devices so that the best performance can be matched across all patient demographics and surgeons. At the other end of the spectrum, there are still major unmet clinical needs to treat MSK diseases, requiring improved diagnostics and earlier intervention, as well as improved methods of pre-clinical testing. Across the whole spectrum, there is a need for improved stratification to better match patient and intervention, earlier diagnosis to enable early-stage treatment, as well as better outcome monitoring and use of data to identify where the major issues are.

To address these needs, a number of existing and emerging technologies could play a role.

- To improve preclinical testing, there are opportunities for the development of physiological pre-clinical testing methods and for combined physical and computational testing approaches, for example to examine more realistic ranges of variables.

- To deliver more quantifiable outcome measures, technology for instrumented prostheses and monitoring devices is emerging and the potential to mine (big) data to identify problems, and define criteria for stratification. These developments could also lead to improved design tools that can identify the clinical need and design to that requirement.

- The need for improved health screening and early diagnostics requires cost-effective technology solutions to enable political commitment and achieve high uptake.

The major barriers to translation included the difficulty in obtaining funding at the first translation gap ('valley of death') between academic research and industrial investment. The need to chase investment when a device or product was still at a research development stage appeared common, leading to missed opportunities (where investment was not obtained) or conflicts between investors demanding commercialisation and the need to acquire more robust evidence for long-term uptake of the product. The complex funding landscape in this area, with limited opportunities for sustained investment (but many different funders offering usually small grants) was also identified as being a barrier.

Recommendations to overcome these barriers included the development of a more coherent funding structure along the translation pathway, matched with better expertise to help define the translation route and assess the health economics/ potential cost-effectiveness of the proposed technology at an early stage in the research.

The regulation of implants and physical devices also presented challenges. From the device development point of view, there is difficulty in navigating the regulatory landscape, and uncertainty in the regulation of emerging product lines. There was also a sense that the hurdles were becoming higher which was stifling innovation. From the regulator point of view, there are challenges in dealing with the emergence of new technologies, where standards are not keeping up with devices, and a need for more clarity in the evidence requirements for placing products on market and for post-market data (i.e. full life cycle data: R&D, trial, withdrawal, in service). There is currently a divergence between research, where all of the parameters need to be tested, and compliance which requires only the 'bare minimum' sets of parameters to be examined.

Recommendations to overcome these barriers:

- There is a need to identify emerging technologies and markets early on and define their requirements, necessitating more involvement by regulatory bodies in the innovation process.

- There is a need for investment in the regulation in parallel with investment in the research, for example through greater dialogue and secondments between regulators and academic research groups.

Breakdown of questions and responses

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1. What are the key unmet clinical, industry, market, regulator, user needs and the opportunities for business and service improvement from an industry, clinician and patient perspective?

The key unmet needs were considered in relation to the level of maturity of the current clinical interventions:

Most established interventions

- Example: Hip replacement: highly successful but shows variation between surgeons and patient demographics.
- Needs:
    - To match the performance of the best centres across all hospitals/surgeons – i.e. mechanically robust devices delivering repeatability in performance across the patient population
    - To address the needs of the Asian market (different patient characteristics, different activity profiles to the West)
    - To address the changing demographic being treated – durability and longevity issues
    - All of the above require improved patient stratification.

Less successful existing interventions

- Examples: Total knee and spinal disc replacements where there are high patient dissatisfaction levels.
    - Needs: To determine where the problems lie with existing technology (e.g. in the implant, the surgery, the

rehabilitation etc.) because current outcome measures are not sufficiently sensitive or quantifiable
- Example: Orthotics
    - Clinical needs: development of personalised devices: lightweight, minimally invasive, easy to use devices with minimum time (hospital stay or wait for manufacture), that restore normal independent life.

Emerging or future interventions

- Examples: Ligament/tendon reconstruction, spinal interventions for disc degeneration, multiple tissue reconstruction/regeneration.
    - Clinical needs: ligament/tendon reconstruction e.g. ACL and rotator cuff and Achilles tendon are still basic and require long rehabilitation; spinal fusion has a need for bone in-growth;
    - Earlier diagnosis to enable earlier interventions examples: avascular necrosis, disc degeneration: by the time these are identified it is too late for interventions.
    - New preclinical testing, standards and regulations for new products, which pose challenges in terms of regulation of more complex products, e.g. combination products, multiple tissue reconstruction/regeneration, inclusion of biologics etc.
    - Clarity in evidence requirements for regulation: for placing products on the market and for post-market data e.g. life cycle data (R&D, trial, withdrawal, in service).

Across all intervention types

- need for improved stratification to better match the patient and the intervention,
- earlier diagnosis to enable early-stage treatment
- better outcome monitoring and use of data to identify where the major issues are.

2. How might these be addressed through, and what opportunities do these create for the development and translation of new technologies and improvement of existing technologies?

(Also includes discussion of the opportunities for research and translation that are linked to or associated with the other four themes; the opportunities arising from research and advancement of knowledge and technologies in other areas and opportunities arising from major breakthrough in science and technology in the last decade).

- Improved preclinical testing. There are opportunities for the development of physiological pre-clinical testing methods that are more realistic than current ISO standard material and cell response tests. There is also a major opportunity for combined physical and computational testing, for example using stochiastic approaches to examine more variables
- More quantifiable outcome measures (beyond survey type questions). Examples:
    - instrumented/smart prostheses and monitoring devices
    - Technological solutions to mine (big) data to identify problems, and define criteria for stratification. Several issues were also identified:
        - problems with missing data if reliant on clinical input (e.g. from surgeons), which could bias results
        - the potential to derive 'any conclusion you want' from the larger amounts of available data: the identification of poor performance only becomes useful if it can be used to improve things by changing practice/devices etc.
    - Improved design tools that can take the need and design to that
    - Improved health screening:
        - Barriers in introduction due to short term expense vs. long term saving – difficult policy to implement politically, but health screening is needed for earlier intervention.
        - Cost-effective diagnostics
        - Improved stratification.
- New technologies:
    - Development of personalised structures, using technologies such as additive manufacture and resorbable materials
    - Technology to standardise bedside manufacture to tackle issues of robustness
    - Smart implants that respond to the environment e.g. by releasing antibiotics
    - Improved instrumentation/robotics to tackle surgical variation (but must identify what is optimum first).

3. What are the key gaps in knowledge, that are acting as barriers to translation and what are the important research

questions that need to be addressed and the areas of knowledge and technology that need to be addressed? Are there any systematic barriers to advancement of knowledge and translation of technology in this area that need to be addressed?

Funding/investment barriers and how these might be addressed:

- Current pressure to chase investment too early, without long term support:
    - Difficulties in securing long term commitment
    - Valley of death – lots of different short-term funding streams
    - Still at R & D phase when investor become involved – conflict between investors needs and the acquisition of further evidence
    - Lack of relevant advice, e.g. understanding of health economics, at this stage: does this exist on site at universities (e.g. in business schools?).

- There is a need for better support (both financial and in the provision of expertise) along the development pathway to provide:
    - Better definition of the translation route earlier on
    - Better understanding of cost-effectiveness/ health economics earlier on
    - Competent expertise between completing basic science and the start of translation
    - More joined-up funding across the translation gap.

Regulatory requirements, barriers and how these might be addressed:

From the device development point of view, the barriers were identified as being the difficulty in navigating the regulatory landscape, and the uncertainty in the regulation of emerging product lines (e.g. combination products). There was also a sense that the hurdles were becoming higher, which was stifling innovation, for example in the development of new materials. From the regulator point of view, there are challenges in dealing with the emergence of new technologies, where standards are not keeping up with devices and a need for more clarity in the evidence requirements for placing products on market and for post-market data (e.g. full life cycle data: R&D, trial, withdrawal, in service). There is currently a disparity between research, where all of the parameters need to be tested, and compliance which requires only the 'minimum' sets of parameters to be examined.

- There is a need to identify the new emerging technologies and markets early on and define their requirements. This requires more involvement by regulatory bodies in innovation.

- There is a need for investment in the regulation in parallel with investment in the research – examples included the use of secondments from academia to MHRA to ensure two-way learning (researcher about process and regulators about emerging technology) from the start of innovation so that the regulation can be developed in parallel.

Other barriers

IP

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A number of IP issues were discussed. In biomaterials, there were conflicting needs to develop innovative materials to be attractive for funding, but a busy IP landscape and regulation is making it easier to use materials that are already in use. The conflict between patenting and publication was also raised, and the difficulties in gaining investment to take on patents which had been submitted at an early stage of research.

Clinical

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Clinical validation is very slow, with long time lines for peer reviewed clinical studies, and often too few trials taking place to produce the evidence needed. There were also issues with modest clinical adoption of products, with an example given where surgeons preferred an alternative technology despite the inferior technology evidence. It was recommended that clinical engagement take place earlier in translation to avoid later adoption issues.

Technical

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Identification of failure modes earlier would enable these to have been tested for – improved pre-clinical testing

Difficulty in sourcing GMP approved materials – better advice/sourcing of technology earlier in the translation pathway.

Ruth Wilcox

REGENERATIVE THERAPIES AND DEVICES

There is an opportunity for support to be provided to researchers to get proposals to desired level for translational funding

Theme lead:
Eileen Ingham, Professor of Medical Immunology, University of Leeds

Attendees:

- Graeme Howling, Technology Innovation Manager, Medical Technologies IKC - University of Leeds
- Kenny Dalgarno, Sir James Woodeson Professor of Manufacturing Engineering, Newcastle University
- Rachel Williams, Professor of Opthalmic Bioengineering, University of Liverpool
- Shervanthi Homer-Vanniasinkam, Vascular Surgeon, Leeds Teaching Hospitals NHS Trust
- David Farrar, Science Manager – Biomaterials, Smith & Nephew UK Ltd
- Antony Odell, CEO, Tissue Regenix Group PLC
- Jacqueline Barry, Head of Regulatory, Cell Therapy Catapult
- Stephen Simpson, Director of Research, Arthritis Research UK.

Summary of discussion

The discussions were largely limited to medical engineering technologies, i.e. regenerative devices which are regulated as medical devices and/or devices which can be used to deliver minimally manipulated cell therapies by the medical devices route. The discussions focussed initially on understanding why more of the research in regenerative therapies and devices funded at TRL 1-2 fails to progress to clinical adoption. The discussion was broad ranging, from barriers to translation of a product to commercialisation and market, through to barriers to clinical adoption of an approved product. The key recommendations that arose from the discussions were

- Academic researchers engaged in applied research in this theme should engage with all stakeholders (clinicians, patients, manufacturing industry, regulatory bodies, healthcare commissioners and health economists) at the earliest stage of the research.
- Researchers need to know who to go to. The Cell Therapy Catapult provides this for cell therapies but there is a gap for regenerative therapies/ devices which do not contain cells. Recommendation; CTC to broaden remit or Acellular Therapy Catalyst.
- There is a need for education of stakeholders (RCUK, NGO`s, clinicians, academic researchers) in aspects of translation (product development, manufacturing, regulation, health economics, reimbursement). Linking "science know-how" with "translation know how" which

crosses academic disciplines. This is perhaps an opportunity for the Wellcome Trust.
- Application forms for calls for translational funding in regenerative therapies should include sections on all aspects of the translation process and "translation funding" should be available within grants for researchers to engage with e.g. health economists and regulators plus to e.g. evaluate the reimbursement landscape. Translational awards should be stage gated. (Recommendation for funders)
- There is an opportunity to help the regulators understand emerging regenerative therapies and devices. Academics/ clinicians/ industrialists with appropriate experience should be influencing the regulators and supporting them to take risks.

Specific questions posed and responses:

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1. What are the key unmet clinical, industry, market, regulator, user needs and the opportunities for business and service improvement from an industry, clinician and patient perspective?

There is a range of unmet clinical needs for regenerative devices that medical engineering is addressing in the cardiovascular (vascular grafts, cardiac valves) and musculoskeletal systems (cartilage repair/resurfacing, ligament reconstruction, meniscal repair/ replacement, non-union fracture healing, bone loss in revision surgery), wound healing and ophthalmology (devices for delivery of cells). It is important to note that regenerative devices are already in clinical use and second generation technologies are proving that attention to the biomechanical and immunological properties of the device has distinct patient benefits.

The major clinical and market needs are for regenerative devices that are available "off the shelf" at competitive costs and for regenerative devices that can be delivered minimally invasively.

From a user-need perspective, regenerative devices that have a short time to repair the damaged tissue, yet maintain their strength and function is essential since the user is keen to resume a normal, independent life.

From an industry perspective, reimbursement remains a significant challenge to regenerative medical devices and this will continue to limit their widespread clinical adoption, no matter how compelling the clinical case for use. This is because the benefits are primarily long term and the health economic mechanisms to value this are not widely recognised as yet by the payers. Clinical acceptance varies by disciplines, since there are differences in the metrics/ timelines for demonstration of clinical utility. The stratification of patients is key for higher-cost treatments, since targeted rather than indiscriminate use will become a pre-requisite for reimbursement/ clinical adoption.

Examples of innovation/ technology whether or not successfully translated

Experience indicates that it is easier to translate regenerative devices into the market compared to cell-based therapies, provided that the product is "simple". Products that are overly complex fail. Examples of this include (a) the successful translation of modified silicone tamponade agents to replace the vitreous in the treatment of retinal detachments and the failure to translate a more complex product incorporating silica nanoparticles due to cost (b) successful translation to the EU market of a simple, resorbable polymer scaffold for cartilage repair but the failure to translate a fully tissue engineered cartilage for technical reasons of scale-up and regulatory complexity associated with a cell-based product.

For a development company, a wide platform that can encompass a number of very varied applications is attractive. An example of this is the dCELL® technology, developed at the University of Leeds. Here the first priority was to demonstrate that the technology worked in clinical practice and was approvable by a regulatory body (demonstration of commercial skills). Although this first product did not represent a significant market opportunity, having achieved this enabled the company to raise additional funds to focus on products with multi-billion dollar market potential. Maintaining a network of clinicians and academics enabled the launch of a second product in the US market which has received significant reimbursement approvals (product launch & reimbursement strategy). Key to accelerating/ expanding the business opportunity is the recruitment of industry-experienced specialists. Key to demonstration of the breadth of the platform technology and differentiation from other technologies is continued collaboration with healthcare providers and academic researchers.

Key factors in success are understanding the regulatory pathway, the need to understand the design of the clinical study needed (how efficacy will be measured)

and likely cost (vs gold standard) and time vs expected financial return (size/ value of the market).

Barriers to the advancement and translation of technology in the regenerative therapy space include support along the development pathway, addressing regulatory issues, cost effectiveness and particularly health economics earlier plus better designed clinical studies

2. How might these be addressed through, and what opportunities do these create for, development and translation of new technologies and improvements of existing technologies

Challenges

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- There is tension between RCUK and RCUK peer reviewers with regard to funding in the area of translational regenerative therapies. Whilst blue skies fundamental research must continue to generate new knowledge, if the funders wish to support projects that will go on to progress from TRL 2 to TRL 5 the nature of the application forms and criteria for funding will need to be considered to take account of a wider set of issues to be addressed and the views of wider stake holders. EPSRC currently mainly supports research at TRLs 1-3, with advancement of technology to TRL 3 to 5 being supported through special schemes such as Innovation and Knowledge Centres and Impact Acceleration Accounts. The current peer review system has been established for lower TRL discovery science and fundamental research and may need further modification to support research to support translation at TRLs 3 to5.
- There is a need to connect translational know-how with science know-how (e.g. Arthritis Research UK collaboration with Medical Technologies IKC).
- Regulatory bodies and healthcare commissioners do not always know how to deal with regenerative therapies.
- How do you get new technologies into the hospital? Clinicians find it difficult to try out new approved products. The process is complex and time consuming. Even when a product has made it onto the market, e.g. with CE mark in Europe or FDA approval in the US, this does not mean that the product will be used, even if it does address a key unmet clinical need. The issue of reimbursement has to be addressed in all individual countries with associated health economic assessment. Individual countries want clinical data from their own patient populations. Challenges are increased due to biological variation in regen med products (even acellular).

Opportunities

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- There is an opportunity for more focussed translational calls which are judged on different criteria. Sections in the application for funding related to translation should be included (e.g. for Health Economics, Clinical Engagement, Regulatory Issues, Reimbursement Landscape, Evaluation of Clinical Efficacy, Costs of Goods, Manufacture, Storage etc). These should not just be tick boxes or idealised pathways to impact, but real evaluation criteria. Applicants need to be honest and not make false claims regarding TRL and timescales to market/ clinic. Funders should fund activities related to these translation barriers. Funders also need to understand the barriers, as do the peer reviewers. Stage gating of grants is needed with defined stop/go decision points.
- Clinical engagement groups to cover the views and needs of multiple clinicians including clinicians with experience of clinical adoption of new products (an individual clinician may be passionate about a new products but may have no idea how to get the product into clinical use).
- The Cell Therapy Catapult (CTC) provides support for researchers engaged in the development of cell therapies on regulatory issues, health economics, process development, reimbursement, clinical adoption and engagement with NICE. However, acellular products (regenerative medical devices) fall outside the scope of the CTC. Is there a need for a Catapult for regenerative devices/medical devices/technologies?
- A potential opportunity for the gap to be filled by NGO charities such as Arthritis Research UK, would require education of NGO funders in translational and product development processes.
- Opportunity for support to be provided to researchers to get proposals to desired level for translational funding (IKC PoC projects; Welcome Trust Translation Projects) .

3. Key factors which need to be addressed for successful clinical adoption of regenerative therapies/ devices (key gaps in knowledge acting as barriers to successful translation)

- Early engagement with the right clinicians
- Early engagement with Health Economists

to understand costs vs benefits
- Early engagement with regulatory bodies to understand the regulatory pathway
- Early engagement with industrialists whose expertise is product manufacture
- Understand how product will be sterilised/stored
- Understand clinical trial needs early
- Understand the clinical need to be addressed and how efficacy will be measured (outcome measures) as well as size/value of the market [in comparison to gold standard products)
- Understand the reimbursement landscape [different in different countries]
- Due diligence prior to investment in opportunity (TRL-2 to TRL 5). Commercial/user evaluation
- Ability of the development company to demonstrate commercial skills and commercial differentiation in a crowded market
- Regular evaluation/review with users and clinicians.

4. What are the opportunities for research and translation that are linked to, or associated with, the other four themes?

Opportunities for translation of research in this area vary by clinical discipline or even sub-discipline. Some clinical disciplines are more conservative than others (for example in orthopaedics, arthroscopists are earlier adopter's than orthopaedic surgeons). There are opportunities:
- For treating some diseases with regenerative devices at an early stage (e.g. prevention of osteoarthritis), but in other disciplines (e.g. cardiovascular and ophthalmology) early intervention with regenerative devices prior to the manifestation of disease symptoms may not be appropriate.
- to connect the right academic researchers from different multiple disciplines with the right clinicians perhaps through "meet the engineer" or "meet the clinician" sessions which could be co-ordinated by funders. UKRMP have been attempting to do this for cell therapies. Other EPSRC research centre initiatives are supporting networks to engage academics with clinicians.
- for linkage with Imaging, Sensors and Diagnostics themes to (a) stratify patient populations such that regenerative therapies/devices are targeted to right patient at the right time (b) track the clinical outcome of a regenerative therapy/device.

There is an opportunity for linkages to develop better animal models, which are generally very poor.

There is an opportunity to help the regulators understand emerging regenerative therapies and devices. Academics/clinicians/industrialists with appropriate experience should be influencing the regulators and help support them to take risks. This is an opportunity to develop better understanding from both sides. Currently the MHRA will not tell you what you need to do to get a product approved.

Evidence and examples of good practice:

- Don`t "run away" from the scary bits
- Talk to research regulators early in the research phase. Gain knowledge of the risks/issues that need to be addressed. Don`t assume they need e.g. animal data, there may be other methods of safety and efficacy testing
- Define the clinical need, plan and understand the whole process, pre-clinical studies, animal trials, clinical trials, regulatory approval etc.
- Include reimbursement landscaping in funding proposals.

5. What are the opportunities arising from research and advancement of knowledge and technologies in other areas (8 great technologies and other industry sectors).

- Common platforms/funding to share the challenges in the areas of regulation/health economics/reimbursement in regenerative therapies with industry involved in the dialogue. NGO`s involved through the Association of Medical Research Charities AMRC
- Potential opportunities for CTC to expand training offered to academics on health economics and reimbursement
- It is important not to re-invent the wheel. Learn from what has been done in the past.

Eileen Ingham

IMAGING

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Developments in medical imaging can also transfer to help support discoveries in other fields and disciplines

Theme lead:
Alison Noble, Technikos Professor of Biomedical Engineering, University of Oxford

Attendees:

- Rob Tolhurst, Departmental Manager, King's College London
- Sebastian Ourselin, Professor of Medical Image Computing, University College London
- Chris Taylor, Associate Vice President Research, University of Manchester
- Steven Williams, Professor of Imaging Sciences, King's College London
- Phil Conaghan, Professor of Musculoskeletal Medicine, University of Leeds
- Lorna Thomson, Director of Research Strategy, King's College London
- Katie Daniel, Senior Healthcare Technologies Manager, EPSRC.

Imaging is often considered a mature research field, with the UK considered a major international strength in technologies for medical image acquisition (for instance MRI, optical microscopy) and medical image analysis (including image quantification, object detection, and co-registration). Imaging is becoming quantitative and volumetric. Additionally, the UK academic imaging community has an excellent track record of creating medical imaging spin-out companies, some of which have grown to UK-based medium size enterprises, and others have been bought by large companies. Relationships between academic groups and big industry are generally good in the UK. Arguably, strategic partnerships between medical imaging academic groups and industry are much stronger and more widespread in Europe due in part to proximity and a greater focus on establishing strategic partnerships (as opposed to one off projects which current funding models encourage). There is considerable clinical pull for new imaging technologies to support radiologists and clinicians in their day-to-day work to generate the high resolution images and videos they need to look inside the body for diagnosis, to guide surgery and therapeutic procedures, to monitor conditions over time and to automate image interpretation tasks.

However, maturity does not equate to a lack of major areas emerging in the field. In acquisition, the economic drivers to reduce healthcare costs, has resulted in a need for new advances to lower the cost (time and capital) of imaging through the development of cheaper, often portable, devices, quicker acquisition protocols and making technologies easier to use by a non-expert. Major new

opportunities are also being generated by "Big Imaging" data and the need to analyse (using machine learning) both very large volumes of image data but also complex data patterns within a data set and across population datasets. In the latter case, the potential to both discover new clinical biomarkers and provide radiologists and other clinicians with new tools to support clinical decision-making is likely to dramatically transform radiology and the whole of clinical medicine in the next decade. The role of the radiologist is changing due to technological advances and this trend will continue. Imaging technologies are often developed by close collaboration between engineers and clinicians and are technologies that can be fairly rapidly translated into clinical practice to demonstrate real impact on a relatively short timescale.

Specific opportunities and challenges

Big imaging data

Big Imaging Data generally refers to the analysis of the complex patterns in large population imaging data. It is a new area enabled by the availability of large digital datasets, advances in machine learning algorithms, and wider availability of high performance computing. Big imaging data and its relationship with 'omic' data is an exciting embryonic area which is likely to deliver results in the next decade or two. This area does however present technical and practical challenges. Technically, challenges relate to the need to annotate data for supervised learning which is currently largely a manual process. Most studies are currently done on clinical research cohort data, which can have different properties to real world clinical service data (missing information and incorrectly labelled data, lower and more varied quality, heterogeneity of conditions). Practically, access to real world (NHS) clinical data is challenging, as is sharing data between sites (academic and industry). This is both a problem for sharing data within the UK and an even greater issue if working with other international groups. Generating the large imaging data sets that image analytic methods need is expensive, and prohibitively so for a single site in many cases. Simplifying data governance and developing easier processes to share data are essential if the potential in this area is to be realised. The UK has the potential to be an international lead in this area. Persuading NIHR to make datasets available from the NHS is a priority and would provide a considerable step towards this.

Efficient imaging

There is a need to balance clinical benefit with economic benefits and clinical work flow. This translates to a need to put imaging to more efficient use and avoid expensive modalities. For instance, work is being done to consider where ultrasound might replace MRI or CT. Few academic imaging technology research projects link technology development to routine clinical practice. Health economic studies on imaging are largely absent and would help to inform where further research should be focussed. The TOHETI project (http://toheti.org/), a Guy's and St. Thomas's trust (GSTT) funded project was highlighted as an example project but these kinds of projects are not widely supported by Research Councils.

Industrialisation of medicine

There is a need to move away from intuitive medicine and allow imaging technology to support non-expert healthcare workers to deliver diagnosis and therapy. This requires de-skilling imaging to ensure it can be more widely used. Key questions here are how to measure intuitive 'knowledge' and to define diagnostic and therapeutic tasks which would benefit from industrialisation.

Imaging the symptom

Current practice is to image anatomy, function or metabolism. We have poor understanding of how to image symptoms such as chronic pain (general, or specific to say the knee).

Computational modelling and imaging

Imaging has for some time supported the development of the field of computational modelling in biomedicine as it provides the personalised imaging data (anatomical and functional and typically from MRI and CT) specific for creating a real model. However, models produced to date are relatively simple, focused on static characterization (rather than longitudinal) and few have yet been shown to be useful for predictive medicine in practice. There is a need for a greater clinical engagement in finding roles for computational modelling. Computational modelling, with its focus on supporting clinical decision-making based on data from an individual, differs significantly from the predictive approach advocated by emerging data-driven approaches of machine learning and it will be interesting to see whether and how the two paradigms converge to support clinical decision-making in the future.

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SOME OF THE NEW TECHNOLOGIES BEING DEVELOPED AIM TO SUPPORT NON-EXPERT USERS OF IMAGING OUTSIDE OF RADIOLOGY DEPARTMENTS WHICH FURTHER QUESTIONS THE ROLE OF A RADIOLOGIST IN THE FUTURE

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The changing role of radiology

There are few radiologists doing academic research in the UK, which can make it challenging to advance the clinical translation of new methods into practice. Some of the new technologies being developed aim to support non-expert users of imaging outside of radiology departments which further questions the role of a radiologist in the future.

Adoption of imaging technology in radiology practice is being driven by the business case, rather than whether the technology is necessarily the best technology on the market. For instance, existing 1.5T MR scanners do the bulk of work in UK hospitals, but 3T and 7T scanners are being pushed to the fore for research and may have preference for grant funding. A question here is whether more research should be done to determine how existing 1.5T scanners can deliver 'big data' for research. Research has been done, for instance, to tailor MR scanners to more specific areas of the body to economise on scanner size. Extremity scanners are deemed good for research but are not yet widely used in hospitals. There are parallel questions one could ask for other imaging modalities such as CT and ultrasound.

Impact of imaging more widely

Areas we did not discuss in depth, but which are major areas of application of clinical imaging, include image-guided therapy, surgery, and radiotherapy, and imaging as a treatment – photoacoustics and theranostics.

We also did not discuss biological imaging in depth but recognise it as an area of UK strength. Here the technical interests are a little different and include acquisition and analysis to support high throughput screening, the small experiment and how to image structures in three dimensions.

Imaging is a cross-cutting technology that is not restricted to clinical and biological applications, and developments in medical imaging can also transfer to help support discoveries in other fields and disciplines (especially veterinary science, materials science but in some cases any area of imaging application). Developments in related areas of imaging sensor development, signal and image processing, computer vision and machine learning also transfer to support advances in medical imaging.

Connections with the Crick and Alan Turing Institutes are also very relevant going forward to ensure a healthy exchange of research ideas and knowledge. Mechanisms need to be put in place to ensure that the investments in these major initiatives support the development and delivery of next generation medical imaging solutions.

Taking things forward

Models for funding

It is difficult to get early translational research funded via current funding mechanisms. EPSRC tends to support pre-translational proposals. MRC funds clinical trials of more established methods but not engineering refinements which are often needed in early translation. Many technologies and methods are lost in the gap between. There is no mechanism to smoothly move from technology development to translation, which can take 5-7 years to complete. Possible solutions including bridging funding or stage gating (3y+2y model for research then pump priming studies in man as a cross council initiative). This would also allow funders to share the risk of funding. The important thing for academic researchers is that the funding has the potential to be continuous if research is going well and not subject to the uncertainties of timing of follow-on grant awards. It would also be important that such proposals were assessed by an inter-disciplinary panel so various stakeholder views (from academic physical sciences and engineering, medicine, and industry) were gathered in assessment. The Innovate UK/ MRC model for the Biomedical Catalyst scheme was mentioned as a model to consider, which could be relevant for imaging.

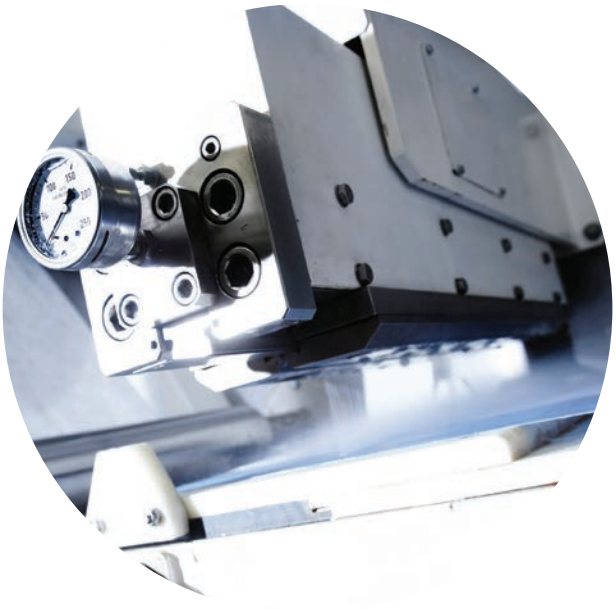
Future workshops

It was noted that attendees were those who are already doing clinical translation so the views expressed did not reflect those who find it difficult to connect with clinicians and carry out translation research. These researchers also need supporting. A workshop focussing on 'Barriers to Translation' might be useful to help articulate challenges for such researchers, as well as to provide education on how to overcome real as well as what are sometimes perceived barriers.

Challenge driven research

It would be interesting to ask the Royal Colleges (say) to come up with the top 10 unmet needs of Radiologists/radiographers and challenge the EPSRC academic community and industry to solve them.

Alison Noble



SURGICAL TECHNOLOGIES AND ROBOTICS

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Big data is central - collecting and centralising data that tells us what strategies we should be using in rehabilitation

Theme lead:

Guang-Zhong Yang, Director of the Hamlyn Centre for Robotic Surgery, Imperial College London

Attendees:

- Damien Lacroix, Professor of Mechanobiology, University of Sheffield
- Martin Levesley, Professor of Dynamics and Control, University of Leeds
- Stephen Smye, Director of Research and Innovation, Leeds Teaching Hospitals NHS Trust
- Annette Bramley, Lead - Healthcare Technologies, EPSRC
- George Trichas, Business Analyst, Wellcome Trust
- Jo Dixon-Hardy, Director of Medical Technology Innovation, University of Leeds.

Key unmet needs (clinical, industry, market, regulator, user) and associated opportunities

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Over-arching clinical needs in this theme include prevention, early intervention and minimally invasive treatment. These provide drivers for precision surgery as part of precision medicine. Surgery could be seen to be at a 'tipping point' between interventions that treat disease to interventions that may prevent disease. Increased longevity and survival after major illness means that many surgical patients have co-morbidities. This drives a need for a system level approach with opportunities for integration of technologies around imaging, sensing and robotics. It was felt that surgical interventions should not be seen as starting with an incision or ending when the patient leaves the operating theatre but that there should be more alignment with rehabilitation and assistive technologies (e.g. from hospital to home environment following a stroke) and a greater emphasis on quality of life. This provides an opportunity to exploit the UK's strength in robotics and surgical technologies, as well as significant potential for adoption and adaptation of technologies from other industries, particularly for establishing synergies for different robotics application areas. The UK now has a more coherent RAS (robotics and autonomous system) strategy through the coordination of the EPSRC UK-RAS Network. Such a synergy will inevitably support the research, as well as training and shared resources in this area.

The need for a focus on making sure the device is doing what its intended to do, rather than providing multiple degrees of freedom was emphasised – i.e. 'simple enough to be reliable'

and 'cost-effective'. A potential spectrum of complexity was identified, from complex robotic therapy in clinic through to simpler devices for use in the community. The development of assistive robotics technologies was discussed and this is an area that can attract significant growth in future years. For assistive robotics, there is a need to address the challenge of usability stigma and practicality in the home environment. This could include approaches that make better use of material science and soft exoskeleton for 'invisible wear'.

Medical device development is a complex field. It was considered essential to think about clinical trials at the outset to ensure appropriate size and scope of trials and that the business cases are strong enough and aligned with NHS price points. Early health economic data is needed to support the technology, to ensure better potential for NHS procurement. 'Frugal innovation' was discussed and the global benefits for producing things at a lower cost and treating more people with the things we have.

High speed adoption was seen as an innovation driver and slow adoption by the NHS a significant challenge. The opportunity for researchers to request funds for health economic assessment from EPSRC was highlighted, as EPSRC is trying to encourage uptake of these resources.

Key challenges and barriers to translation

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- Health economics, cost-effectiveness of technologies and real impact on clinical outcomes are key considerations. While there is a need to find the right level of sophistication and cost for the right point in the patient pathway, robotics as a technology is at an early stage and a full blown health economic study is felt to be premature. There is a need to direct future effort to areas where robotics will make a difference to clinical outcome. There is potential for a health economic pathway analysis for procedures to show points at which robotics would add value (could work with engineering and clinical community to do this)?
- There are big hurdles and funding gaps in the UK in translating technologies to routine clinical use. Current major funding challenges include de-risking early stage technologies and larger trials, as no funder will currently support the latter and industry is averse to funding these. In addition, finding sufficient patients for robot trials is a challenge, although the direction of pushing for smaller, more compact robotic platforms may change this and this is an opportunity that the UK should exploit.
- The vibrant eco-system in the US was discussed. It was suggested that UK funding pots could be sliced up and stage gated to achieve a more productive ecosystem. It was felt to be more important for SMEs to support technology development than big companies, as vibrant SMEs are more likely to take risks. It was suggested that funders could encourage SMEs as partners rather than blue chip companies.
- Effectively communicating the 'exciting-ness' of robotic technology to the engineering community is essential.

Challenging but critical stages of technology development:

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- Progressing technology from a working prototype to large cohort patient studies to commercial product.
- Robust early-stage assessment of potential clinical impact, supported by health economic modelling studies which take into account existing and novel competitor technologies.
- Close collaboration with clinicians and patient user groups, regulatory issues, procurement, clinical adoption, investment for large scale trials and cross-theme interaction.

Opportunities

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- Robotics could make a real difference in neuro, endovascular, oncological, and orthopaedics surgical procedures. E.g. in onological surgery there is opportunity to compare robotic surgery to other therapies and to combination therapies
- There is a unique opportunity in the UK for a research focus moving towards smaller, compact devices for surgery which will address the cost-conscious mind-set
- There is an opportunity for research funding of devices (e.g. China sees the UK as a serious competitor globally) and this may require a collaborative effort with industry
- The EPSRC Engineering Theme has an emphasis on robotics and it is important to ensure healthcare challenges are integrated
- Assessing where proposed technologies sit in patient pathways (difficult but essential)
- Understanding competitor technologies, the advantages of proposed technology and where it sits in a cost-pressured system
- A cross-theme interaction with e-health is crucial for devices. There is a need to monitor health of people and how that is changing over time
- Big data is central. Collecting and centralizing data that tells us what strategies we should be using in rehabilitation. The ability for clinical records to be more accessible

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ROBOTICS COULD MAKE A REAL DIFFERENCE IN NEURO, ENDOVASCULAR, ONCOLOGICAL, AND ORTHOPAEDICS SURGICAL PROCEDURES. E.G. IN ONOLOGICAL SURGERY THERE IS OPPORTUNITY TO COMPARE ROBOTIC SURGERY TO OTHER THERAPIES AND TO COMBINATION THERAPIES.

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- The ability to join up data, e.g. between primary and secondary care, would make a big difference.
- Health economics plays a central role, both in terms of an understanding at the outset of technology development and in the longer term. There is a need to be smarter about the early stage health economic assessment of the value of the technology (including the views of clinicians). A more joined up effort is required at a national level
- There is a need to identify surgical applications where imprecision is a problem (e.g. prostate, neuro, endovascular). Clarity is needed on where lack of precision is reflected in poor clinical outcome, e.g. ACL
- There is scope to improve on pre-operative planning and opportunities in theatre
- Conducting clinical evaluation in the NHS
- Opportunity for funders to sign-post applications for different TRLs. The group identified EPSRC for TRL 1–3, NIHR for 4–5, Innovate UK for TRL 5 and industry for TRL 6+
- The need for different skills, funding streams, etc. to be on board from the outset was emphasized, aligned with a need to generate and maintain excitement, focus and a community feel.

Exemplars

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- Assistive robot for use by adults with stroke and children with neurological conditions such as Cerebral Palsy
- NIHR HTC in colorectal therapies, anastomotic leak detection, chemi-luminescence for bowel cancer, and optical biopsy of polyps.

A white paper by UK-RAS Network on the future roadmap of surgical robotics was tabled during the meeting (email g.z.yang@imperial.ac.uk for a copy). Many of the points, in terms of future research directions, as well as commercial, regulatory, and healthcare policy are discussed.

Jo Dixon-Hardy

E-HEALTH SENSORS AND DIAGNOSTICS

Technology can potentially be developed quickly, but innovation in process and systems can take longer

Theme lead:
Duncan Graham, Research Professor of Chemistry, University of Strathclyde

Attendees:
- Theo Arvanitis, Professor of E-Health Innovation, University of Warwick
- John Fisher, Deputy Vice Chancellor and Professor of Mechanical Engineering, University of Leeds
- Cassie Doherty, Director, IP Group
- Bruce Campbell, Chairman, NICE Medical Technologies Advisory Committee
- Philippa Shelton, Policy Advisor, Royal Academy of Engineering.

Notes taken by: Jane Wilcox, University of Leeds

This discussion group looked at a number of questions in relation to this theme focusing on barriers to greater translation and what could be done to try and encourage higher success rates from the research community resulting in clinical deployment.

The challenge of translation of this technology

The main outcome from this discussion was agreement on the need for a value proposition to be created as a pre-requisite for research to support the translation of technology that is relevant to E-health, sensors or diagnostics.

The nature of the value proposition should encompass a number of different considerations including:
(i) patient expectations and outcomes,
(ii) the service expectations (the NHS or perhaps reimbursement out with the UK),
(iii) society's perspective and finally
(iv) the sustainability.

The group considered that a clear value proposition would encourage researchers to think about the end application, the clinical pull and the mechanisms that might achieve translation from the research idea and findings to something which would be used by clinicians and patients, and how the technology would be incorporated into the healthcare pathway, processes and systems. It is important to consider whether the research and technology enables new things to be done (disruptive) or for existing things to be done differently (displacement). While in this area, technology can potentially be developed quickly, innovation in processes

can take longer and can act as a barrier to adoption of technology innovation.

An example was given by BC where NICE had supported the publication of a series of papers by surgeons on how to introduce new surgical techniques into clinical practice, through various stages involving different types of research and reporting. Nothing of this nature exists for diagnostics and the group considered that a defined sequence of research requirements would be useful, in addition to creating a value proposition, to underpin the design of the research. Such an approach would improve the chances of success of translation into clinical practice.

The group felt there was an opportunity to encourage the community to develop a work flow of items to consider when developing value propositions. These could include the unmet clinical need, the nature of use, the current industry activity and market, the potential return on investment and the expected investment required for commercialisation. In addition there are a host of other factors relating to this technology area and which need to be robustly considered, pulled together and disseminated across as the research community as an aid to translation.

The barriers to translation

Some of the potential barriers to translation not only include financial and regulatory concerns but also, importantly, the cultural change required for technology innovation translation and adoption. The cultural change requires involvement of researchers engaging with clinicians earlier in the research and innovation process. Clinicians need to keep an open mind about new technologies and to consider in a positive light the opportunities made available to them through new technology. Healthcare expectations are changing. The UK is still very NHS-focused rather than patient driven. As a research community, can we encourage funders to aid in the translational pathway by diverting some more resource into translation through documents such as this? Would including a value proposition as part of a research grant encourage this and can the Research Councils and funders play a greater role in joining up dots between promising emerging technologies and appropriate end user engagement?

Future opportunities include

Looking ahead there are many exciting opportunities on the horizon for this thematic area including:

- Improvements in the scale of storage and speed of transmission of analytical data,
- the emergence of next-generation sequencing leading to improved molecular diagnostics and, potentially, point of care genomics but again concern was raised in terms of data interpretation
- Wearable technologies are emerging as a new opportunity
- can healthcare borrow from advances in other technological fields such as space exploration or the IT sector?

The main outcome from this discussion group was a strong recommendation for the development of a value propositions to aid thought and planning of research and translation of any diagnostic technology. This would be a very helpful and compelling exercise but it needs buy-in from the different stakeholders, from the research community, from clinicians and from funders of research.

It was felt that a focus on the value proposition would enhance the future degree of success of translation of promising technologies and unite parts of the research community working in this area.

It was recognised that a diverse set of skills, experiences and capabilities are needed to develop a robust and realistic value proposition and these do not often reside in academia or in a single individual but need input from a diverse range of stakeholders.

Duncan Graham

FINAL COMMENTS

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What might come next?

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Where does this workshop and these discussions lead?

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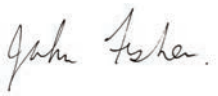
There are diverse views in the academic community about the balance of discovery-led research and challenge-led research. One perspective is that setting priorities based on national importance may over constrain the research agenda through a top down approach. This has to be balanced by views that to create more value from research, there is a need to identify and address the real world opportunities for challenge-led research and advancement of knowledge and technology, derived from the insight of users and to identify and target at the needs of a diverse groups of stakeholders. Specifically, in challenge-led research and research to support the advancement and translation of technology, there is a need for greater precision in the definition of the challenge and this applies to research to support the development of medical technologies.

Currently, an approach to addressing this balance is through broadly targeted calls, which allows the academic community and the peer review community to determine the precise targets and priorities through a competitive process. However, the advancement of knowledge and technology to higher technology levels beyond TRL 1 & 2, requires greater precision in the definition of the research targets and this precision needs to be defined by a wider range of stakeholders. The workshop clearly indicated that if we wish to advance the knowledge and technology, then it will need to become differentiated towards different target products and markets and therefore more precise definitions for these targets and the targeted research needs are required. Is it possible to create this consensus on more precise definitions of research targets to advance knowledge and technology in a collaborative environment with stakeholders?

The workshop discussions indicated that in each of the five thematic areas, there is scope and need for better and more precise definitions for targeted research to support the advancement of knowledge and technology and future product development. There is an opportunity to pursue and progress these further through the Medical Engineering Initiative in collaboration with our stakeholders.

It is recommended that through the Wellcome Trust / EPSRC Medical Engineering Initiative it should be possible to facilitate the establishment of working groups comprising of a wider set of stakeholders in each of the thematic areas identified through the Medical Engineering workshop with the aim of generating more precise definitions of the recommended priorities for each area which will support the advancement of knowledge, early stage innovation and translation of technology.



John Fisher

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