What are the priorities for future success in critical care research in the UK? Report from a national stakeholder meeting

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Abstract

Critical care in the United Kingdom is now well-established in terms of professional status, standards of clinical practice and training, and national audit through professional bodies and government representation. Research is fundamental to the further development and maturation of the specialty, to develop new therapies and technologies, more efficient and effective service organisation, and to improve patient and family experience and outcomes. Critical care research has expanded rapidly in the UK, and now has established organisations and infrastructure to share and develop ideas, through the UK Critical Care Research Forum and similar meetings. In September 2014, the Intensive Care Foundation and Critical Care Leadership Forum hosted a research colloquium to reflect, in part, on achievements, but more importantly plan for the future. With an invited list of participants the meeting explored firstly – the practical delivery of clinical research and secondly – the future financing landscape, from both academic funders' and commercial developers' perspectives. The following article summarises the important 'take home' messages from this meeting and suggests key issues for future strategy.

Keywords

Research priority, critical care, intensive care, critical illness, funding

Critical care in the United Kingdom is now well-established in terms of professional standing, clinical and training standards, and national audit through professional bodies and government representation. Research is fundamental to the further development and maturity of the specialty to develop new therapies and technologies, more efficient and effective service organisation, and to further improve patient and family experience and outcomes. Critical care research has expanded rapidly in the UK, and now has established organisations and infrastructure to share and develop ideas, through the UK Critical Care Research Forum and similar meetings, and to deliver large-scale practice-changing research through the NIHR Clinical Research Network (<http://www.crn.nihr.ac.uk>). The NIHR CRN national specialty group in Critical Care is widely-recognised as being very effective, enabling the effective delivery of a growing portfolio of clinical research studies. Success is visible through the publications resulting from the increasing numbers of high-quality large trials.

In September 2014, the Intensive Care Foundation and Critical Care Leadership Forum hosted a research colloquium to reflect on achievements, but

more importantly plan for the future. A wide range of national research leaders, representing virtually all of the major government and charitable funders, attended and spoke. Senior members of the NIHR delivery network also contributed, along with leaders from industry and academic training programmes. These talks were complemented by presentations from members of the critical care community, reflecting on issues and opportunities specific to our specialty. The aim of this article is to report the key messages of these talks and discussions to the critical care community. We have used notes and discussions to summarise their impressions of the important 'take home' messages. We present suggested key learning points for moving forward.

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What was said?

This report cannot capture in detail the content of all lectures, talks, and discussion. Table 1 lists the invited speakers from outwith critical care, their background, and the key messages we took from their talks and associated discussion.

A number of other contributions were made from members of the critical care community. Professor Tim Walsh (National Lead of the NIHR CRN: Critical Care Specialty) reflected on the impact of the NIHR clinical research network on critical care during the first 6 years of its existence. Great progress has been made, with increased numbers of studies, progressively increasing engagement of ICUs with embedded research staff and infrastructure, and a coordinating specialty group-based organisational structure that is improving access to and efficiency of research. Challenges for the future include maintaining activity through project grants, developing commercial/industry research, and coordinating allocation of new projects according to capacity and likely patient base. A move towards wider use of extended hours of screening and recruitment, including weekends, would likely have a major impact on recruitment. Dr Tony Gordon (ICS Co-director of research) reviewed the potential benefits of large-scale international collaboration, and the need for large trials with sufficient statistical power to detect minimum clinically important differences in outcomes such as mortality. Given the heterogeneity of critical care populations, studies with power to detect important differences in *a priori* defined sub-groups is highly desirable. This is unlikely to be achieved within single countries, especially for specific types of critical care populations. Several projects have already explored the feasibility of international collaboration at different stages from planning through to post-funding participation. Success has been variable. Major challenges that have emerged include the timing and ability to satisfy multiple national funding bodies, and working to different timescales and review structures, potentially with differing research priorities. Sheila Harvey (CTU manager, ICNARC; www.icnarc.org) discussed recent experiences of optimising recruitment into critical care trials. She noted the importance of coordination and communication, and working closely with individual site teams and R&D departments. The NIHR network has offered significant benefits that can reduce the workload of trial management. The shared experience of the various trial units in recent years and multiple investigators with experience of setting up and delivering multicenter trials highlight the need to avoid 'silos' of expertise and to share knowledge and experience. At present we have no generic mechanism of sharing models of critical care research delivery, or core materials such as databases or questionnaires. Professor Gavin Perkins (Co-director of research, ICS) gave a brief overview of

clinical trial activity and successes in the UK, highlighting the exponential growth in activity and key publications. Professor Danny McAuley (Co-director of research, ICS) highlighted the opportunities to develop and realise translational projects linking basic science discovery to clinical benefit. The NIHR schemes recognise this natural progression through its different Medical Research Council (MRC) and NIHR-funded schemes; the MRC contributes funding for the Efficacy and Mechanisms Evaluation programme, which acts as a bridge between basic and clinical research. However, the importance of only progressing to large and expensive phase III trials when both the science and the trial design are as fully worked out as possible is key to both success and value for money for funders. The history of negative trials in critical care highlights the importance of this issue. Dr Nazir Lone discussed the enormous potential for 'big data' to inform multiple aspects of knowledge about critical illness. In particular, these epidemiology approaches may enable better and more efficient trial design, for example through better stratification or adjustment, or for collecting longer term outcomes through data linkage methods. The need for high-quality research training in this area was clear.

Key messages

There were many messages for our specialty from this stimulating and collaborative meeting. The authors have attempted to refine these into some focused issues that may form the basis of future work, and serve to help prioritise where research effort should go. We have grouped these under several headings:

Clinical research question priorities

1. *The community should develop research questions and submit these through the prioritisation schemes, with the aim of some projects being commissioned.*
2. *Research questions must have demonstrated clear importance to the NHS: this may include the views of patients, clinicians, and other stakeholders but must demonstrate clear potential for cost-effective improvements in care.*
3. *Research questions with global relevance that 'stretch' to the developing world are important to major funders (notably the Wellcome Trust)*
4. *Engage with major funders during research question development (especially the Wellcome Trust)*
5. *Research questions that involve or emerge from collaboration with Industry are a high priority: These could emerge at different developmental stages, ranging from pre-clinical basic science to early phase trials, and the design of phase III trials.*
6. *Infection and trauma are UK and global priorities relevant to critical care.*

Table 1. A summary of key points made by speakers from major external organizations who attended the meeting.

Speaker	Overview	Key points
Professor Steve Smye <i>NIHR CRN: progress and prospects</i>	Described the new and evolving structure of the NIHR Clinical Research Networks to deliver research in the NHS, and what the priorities for the future are. Discussion also focused on the specific challenges of critical care research, in relation to complexity, time sensitive recruitment and delivery, and resource heavy protocols.	<ul style="list-style-type: none"> • Expanding access to research for NHS organisations and for individual patients is a priority • Identifying and supporting clinical research leaders, including local University recognition schemes for NHS clinical researchers and the development of trainee networks, is vital to success • Participation in research is often associated with overall higher quality of care in an organization • Working with Industry to develop and deliver research in the UK, and bring fiscal benefit to the UK • The NIHR CRN national specialty group in critical care is widely recognised as being very effective, enabling the delivery of a growing portfolio of clinical research studies. • Maximising the use of UK strengths, such as access to 'big data'. Critical care is particularly well-placed in this regard, given existing networks (including ICNARC). • Focusing effort on precision medicine (previously called stratified medicine)
Sir John Savill <i>The MRC viewpoint</i> http://www.mrc.ac.uk/	Described the role of the MRC in funding, which is still focused on experimental medicine, systems biology, and translational medicine. An increasing focus is on 'precision' medicine, involving a deeper understanding of disease processes and subtypes. There is recognition that research limited to animal models has not translated efficiently, and future work should increasingly utilize human models whenever feasible. Informatics and the use of 'big data' to better understand and model disease is key to the future. This may contribute to precision medicine by enabling treatments to be focused, or provide prediction tools. Informatics has major potential to increase efficiency and effectiveness of healthcare. Collaboration, especially with Engineering and Physical Sciences, is seen as the way to make major steps forward through novelty and maximizing cross-disciplinary knowledge and idea sharing. Avoidance of silos and or isolationism both as a specialty and across specialties is vital. With this in mind it is important to be mutually supportive within a specialty, for example in relation to grant review. A key to future success within a specialty area is promoting and supporting academic training programmes, especially those that provide continuity and enable cross-	<ul style="list-style-type: none"> • Promote and develop interdisciplinary programmes and collaborations, especially with the physical sciences (physics, chemistry, statistics, computing, informatics etc) • Future research should focus on human or 'humanized' models of disease whenever possible • Search for opportunities to use 'big data' and identify important research questions that can use it. • Precision medicine is the key challenge for the future. Identifying methods for delivering precision medicine, for example using biomarkers or informatics, is a key priority. • Key current priorities and opportunities relevant to critical care are infection and trauma • Well-organized academic training pathways, ideally with opportunities to work across disciplines (including out with medicine), should be explored. • Promote and foster mutual support within the community; avoid silos and negative effects of academic competitiveness • Invest effort to identify the 'big challenges' and 'big questions', but ensure they are fundable questions that have potential to deliver measureable healthcare benefits.

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Table 1. Continued

Speaker	Overview	Key points
Dr John Williams <i>The Wellcome Trust</i> http://www.wellcome.ac.uk	disciplinary research training, for example with physical sciences or informatics. Described how opportunities through the Wellcome Trust provide an opportunity for funding. Highlighted that the Wellcome Trust was supportive of programmes designed to provide research training for the highest quality potential academic trainees. The perspective of the Wellcome Trust is to fully characterise disease phenotypes and genotypes, understanding the relationship between health and the environment and potential environmental change, and detailed understanding of complex diseases and complex disease processes.	<ul style="list-style-type: none"> • Work in partnership with industry where possible and appropriate; having an eye to supporting the UK economy. • Develop proposals for high-quality training programmes for the best individuals. • Improve the phenotyping and genotyping of the conditions we deal with.
Dr Andrew Cook <i>NIHR research programmes</i> http://www.nets.nihr.ac.uk	Described the principles of the HTA and EME funding schemes, highlighting that there are commissioned and investigator-initiated schemes. Noted that commissioned schemes have undergone extensive review and prioritisation; these may be the major scheme going forward. Emphasised that investigator-initiated submissions require very strong evidence of importance to progress, and with funding cuts competition and prioritisation in this area would make this route challenging. Also noted that epidemiology and the use of 'big data' are likely to become themes through the HTA and HSDR programmes.	<ul style="list-style-type: none"> • Develop important research questions, with strong justification, and submit as vignettes to be considered for commissioned calls.
Professor Sallie Lamb <i>Chair of HTA CET Board</i> http://www.nets.nihr.ac.uk/programmes/hta	Reflected on what makes a strong research question and a strong application. Noted the results of the James Lind Alliance Prioritisation exercise that was presented at the meeting, and emphasised that although these uncertainties have been developed in partnership with patients, it is vital that research questions are clearly feasible to answer, and also that these answers that will increase knowledge in a way that results in clinically and cost-effective changes to healthcare. Noted also the importance of investigator initiated proposals having detailed background and feasibility work in order to be competitive. This highlights the importance of epidemiology and use of data to inform the importance and design of projects. Discussed the need to develop efficient trial designs that offer better value for money	<ul style="list-style-type: none"> • Ensure the importance of research proposals is strongly justified at application stage. • Ensure answering proposed research questions can be seen to lead to potential clinical and cost-effective improvements. • Explore better methodology in trial and study design that is more efficient.
Dr Oliver Rausch <i>Translational research partnership (TRP) schemes within NOCRI</i> http://www.nocri.nihr.ac.uk/research-expertise/translational-research-partnerships/	NOCRI aims to act as a concierge/facilitator for commercial research within the UK. There are currently three themes, each of which are clusters of academic units providing facilitated access to patient groups for early-stage studies with industry partners. A respiratory TRP exists, whose remit includes asthma, allergy, COPD, cystic fibrosis, acute lung injury, and	<ul style="list-style-type: none"> • Engage with NOCRI to explore possibilities for critical care to benefit or integrate with TRPs

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Table 1. Continued

Speaker	Overview	Key points
Mr Martin Hunt <i>The i4i scheme</i> http://www.nihr.ac.uk/funding/invention-for-innovation.htm	respiratory infection. NOCRI are open to discussions around joining the Respiratory TRP, and supporting development of a proposal for a critical care focused partnership, but this is likely to be limited by funding. I4i provides funding for early-stage healthcare technologies with potential for commercialisation. Support for issues such as intellectual property, patenting, basic business fundamentals are provided, which are often poorly done by healthcare departments and academic institutions. i4i is relatively small but open to applications from any clinical area.	<ul style="list-style-type: none"> • i4i offers an opportunity to fund and progress early technology innovations
Mr Peter Ellingworth <i>Association of British Healthcare Industries</i> Views on device development http://www.abhi.org.uk/	The ABHI facilitates relationships between industry, government, and academic life science departments. Reiterated the perception that many Universities do not optimize this and need to develop relationships with industry in a more sophisticated way. Healthcare inventors and innovators need to move away from the philanthropic enthusiast model towards a more mature business approach from an early phase. This will maximize opportunity and success.	<ul style="list-style-type: none"> • Access expert support and advice early during R&D activity, especially for innovations with commercial potential.
Dr Andrew Bayliff GSK A View from the pharmaceutical industry	Noted that most large pharma, including GSK, have therapeutic priority areas of relevance to critical care, such as infectious disease, immunity and inflammation, and respiratory disease. GSK specifically also note the limited transferability of data derived entirely from animal models. Noted that many pharmaceutical companies have anxiety about critical care based on history of failure and recognition that the heterogeneous nature of patient populations mitigate against successful studies based on syndromic inclusion criteria.	<ul style="list-style-type: none"> • Pharma are interested in critical illness, but work to define phenotypes and knowledge to enable precision medicine are needed.
Professor Jim Neilson <i>Dean for Trainees at NIHR</i> Research training http://www.nihr.ac.uk/funding/funding-for-training-and-career-development.htm	A range of NIHR-sponsored and funded training programmes exist. Some require bidding from regions for posts, and others provide mechanisms for individual fellowships. Support ranges throughout training from Academic Foundation posts, through Academic Clinical Fellow posts, Clinical Lectureships, to senior fellowships and Professors. Critical care and Anaesthesia are relatively under-represented in these schemes. The integration of academic training with clinical training is recognized to be challenging, and not completely resolved, especially in 'craft' specialties such as anaesthesia/critical care. For nurses and AHPs it was noted that schemes are available, and often not fully utilized. In discussion it was noted that a block to nursing/AHP academic training	<ul style="list-style-type: none"> • Develop a strategy to support and mentor potential academic trainees from an early stage. • Engage with training programme directors and Deaneries to facilitate trainees to enter academic training • Nurses/AHPs should be encouraged to enter academic training, but strong mentorship and championing at regional and Trust/organizational level is needed.

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Table 1. Continued

Speaker	Overview	Key points
Professor Jeremy Farrar Director of the Wellcome Trust	<p>was resistance from Trusts to facilitate the time required, even if funded.</p> <p>The WT is reviewing and changing its career development schemes and fellowships, with the aim of being flexible and more inclusive of all disease areas.</p> <p>The WT is keen and encourages early-stage discussion of research ideas, and aims to have an open-door policy with specialties developing ideas for specific projects or programmes. Critical care have not used this opportunity to full effect, but it is common in other area.</p> <p>The WT is enthusiastic for establishing organised and targeted training fellowship schemes that have been developed with the strategic backing of specialty areas. Global health perspectives are very important, and are likely to continue. Projects that address questions with a global health context, which can be tested in laboratories or clinical pathways within the UK with knowledge transferrable into low and middle income countries, would be viewed favorably.</p>	<ul style="list-style-type: none"> • Develop specialty-level ideas with global relevance • Discuss and engage with the WT at an early stage of development • Develop training fellowship schemes with specialty-specific focus, but global relevance.

Types of research

1. *Research using 'big data' is a priority:* In the UK, the acquisition of uniform ICU-level data through national audits offers enormous potential to use 'big data' in research, especially if linked to other data sets that provide additional information about co-morbidity and longer term outcomes.
2. *Precision medicine approaches are needed for critical illness:* The multiple sources of heterogeneity in critical care populations, including demographics, pre-illness morbidity, and acute illness type and severity could all contribute to variable effects, potentially in opposite directions, for similar interventions. Genetic variation could also influence these issues. In addition, the timing of an intervention may be important in a manner similar to the staging of cancer, but within a far more restricted time window.
3. *Better genotyping and phenotyping of critical illness is needed:* This will improve research quality on multiple levels. For example, for precision medicine a better understanding of clinical phenotypes and genotype may improve the timing and choice of intervention; this might involve biomarkers, other diagnostics, and patient pre-illness or acute illness characteristics. For trial design better methods of selecting trial participants, stratification or minimisation at randomisation, or adjustment in relation to outcome comparison could all improve trial efficiency and quality.
4. *Research that involves or engages with the engineering and physical sciences is needed, for example using informatics to model 'big data', or novel technology for diagnostics:* These collaborations have the potential to make major steps forward in understanding and treating disease. Breaking down academic silos to bring experience and knowledge together within and between institutions is needed.
5. *Methodology research is needed:* For example, to improve trial/study efficiency or to enable clinical and cost-effectiveness to be detected within heterogeneous populations.
6. *International collaboration may be needed to achieve adequately powered studies:* This requires work with funders to navigate simultaneous application, prioritization, and review processes.
7. *Translational research, especially with Pharma and Technology industries, is a priority and is currently underdeveloped:* Drivers for this include the need for Industry to access clinical data and academic expertise, and also the potential to attract research funding and IP to the UK.
8. *Develop human models of disease processes wherever possible:* The limited success of animal and cell-based work mean strategies to test novel therapeutics in human or 'humanised' models, for example isolated organs, healthy volunteers, or well-defined groups within ICU populations, should be considered at an early stage.

Academic Training

1. *UK critical care needs a clear strategy to engage clinicians (medical, nursing and allied professional) in high-quality academic training.*
2. *Training schemes are needed in both basic sciences and health services research: the needs of each are quite different, health services research in particular needs strong methodology training.*
3. *Strategies to support 'run through' training, especially post PhD, are needed: future senior academic posts are likely to require competitive fellowship funding (for example from NIHR, MRC, or Wellcome Trust) because Universities will appoint few tenured positions at Senior Lecturer or similar 'entry level'. This will require strong support and flexibility within deaneries for the most promising academic trainees.*
4. *A strategy to provide strong mentorship is needed: National coordination of access to mentorship is needed, especially given the relatively small size of the academic community.*

Research delivery

1. *Maintaining national coordination of the NIHR delivery network is a priority: Key priorities should be maintaining activity within research-active ICUs, and increasing access to research within these and non-research active ICUs. As study numbers fluctuate, careful planning is needed to ensure equitable access to research studies while managing the potentially detrimental effects of study competition.*
2. *Research leadership within Local Clinical Research Network regions and within individual ICUs must be maintained: This will require pro-active approaches and engagement with local R&D and Local Clinical Research Network (LCRN) divisional managers. The role of the local Specialty group Lead is of high importance.*
3. *Generic tools relevant to trial delivery should be shared: These might include unified core outcome datasets, and harmonisation of tools such as core*

daily ICU data, resource use questionnaires, or disability measures. Active sharing of expertise, especially for mentoring new and emerging investigators, should be undertaken.

4. *The UK critical care research forum (UKCCRF) should be further developed: The UKCCRF is the major stakeholder meeting for presenting, developing, and supporting new projects. This is a fundamentally different, but complementary, role to the NIHR CRN. To develop greater standing and effectiveness, analogous to well-known international groups (e.g. CCCTG; ANZICS trials group), this organization/grouping needs to be further developed.*
5. *The critical care community should work proactively to deliver industry sponsored research: This is a high strategic priority for the NIHR and UK government. At present there is relatively little industry-sponsored work on the UK critical care research portfolio.*

Conclusions

This is an exciting but challenging time for UK critical care. An enormous amount has been achieved in the development of the professional specialty, with research playing a major role. The reorganisation of UK research funding and delivery brought major benefits for our community but we are probably emerging from a 'honeymoon period' of success. The conclusions from the Stakeholder event provide a potential focus for future efforts and initiatives.

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