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EDITORIAL

Strengthening acute care in low and middle income countries: The role of clinical research

John C. Marshall, M.D., F.R.C.S.C., F.C.A.H.S., F.A.C.S.
Department of Surgery, St. Michael's Hospital, Toronto, Ontario, Canada

Corresponding author:
John C. Marshall MD,
4th Floor Bond Wing, Room 4-014,
St. Michael's Hospital, 30 Bond Street,
Toronto, Ontario CANADA M5B 1W8
Tel: (416) 864-5225
Email: John.Marshall@unityhealth.to

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We live in an unequal world. Economic inequality is the most obvious manifestation of this global malalignment of resources. In 2018, 26 people held as much wealth as half of the world's population.[1] The American billionaire, Elon Musk, controls more wealth than the entire GDP of Pakistan, a country of 236 million people.[2] Wealth brings power, and the ability to shape a social and political dialog.

Knowledge generated through health care research shapes policy and practice, and the generation of this knowledge is similarly inequitable. High and upper middle income countries representing half of the world's population conducted more than 45,000 clinical trials in 2018. In the low and lower middle-income countries (LMICs) that make up the other half, there were only 6500 trials conducted – 1/7th as many (Figure 1).[3] Low-income countries received only 0.2% of all grants funded by eight major health research funders in 2020.[4] Clinical research improves patient care;[5,6] an inequitable distribution of research activity jeopardizes care.

As we emerge from the global crisis of the COVID-19 pandemic, there is an urgent new focus on clinical research, and on the fundamental role it plays in improving clinical practice.[7] Policy-makers and funders are acknowledging the need to expand global capacity to conduct clinical research: it is critical that we not only enhance overall capacity, but also address the imbalance in the distribution of global research activity. As independent networks of clinician-investigators assume a prominent role in building the knowledge base that informs acute care practice,[8] there is an emerging opportunity and an imperative to expand research in the global south. This requires resources. It also requires a change in understanding of the role research plays in clinical care, and a shift on the part of health care practitioners from being the passive users of knowledge to being the engine that drives new knowledge. This perspective addresses the whys and the hows of building a more dynamic, resilient, and empowered research ecosystem in those parts of the world that are currently under-represented.

CLINICAL RESEARCH: WHY?

Medicine in the 21st century is informed by science. Our understanding of the human body and how it functions comes through basic sciences such as anatomy, physiology, and cell biology. These disciplines enable us to understand how changes in normal function produce disease; observational studies provide insight into the clinical features of these diseases and how they are distributed through patient populations. Identifying effective treatment approaches requires randomized clinical

trials – the most reliable tool to infer causality. During the COVID-19 pandemic, for example, techniques of molecular biology enabled the rapid identification of SARS-CoV2 as the cause of the emerging pandemic. They also enabled an understanding of how the virus interacted with human cells to produce disease, and so pointed to possible strategies to prevent that disease through vaccination or treatments targeting the virus or its interactions with host cells. Large observational cohort studies revealed the distinctive clinical features of COVID-19, including severe acute lung injury and a predilection for thrombosis, and so pointed to other treatment strategies. But it took clinical trials to determine which treatments worked,[9,10] which were ineffective,[11] and which were even harmful.[12] Trials conducted during the pandemic saved more than a million lives as the products of that research were translated into guidance for those caring for COVID-19 patients.[13]

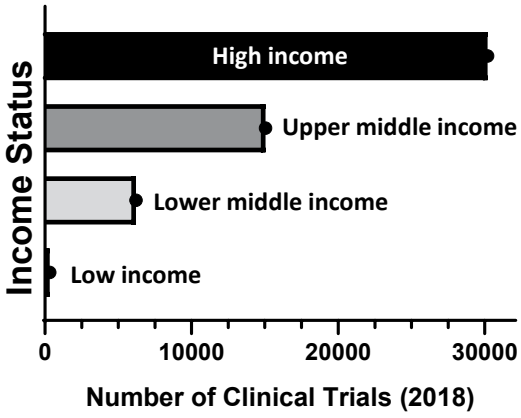

Fig. 1. *Geographic Distribution of Countries of Origin of Clinical Trials Conducted in 2018.*[3]

Research is the foundation of evidence-based practice

Evidence-based medicine is defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients".[14] It is the cornerstone of contemporary medical practice. Evidence-based medicine requires a body of knowledge derived through research; it reflects the questions, priorities, and approaches of those who have led that research. But it raises important questions. Who defines these questions and priorities? Who builds that body of evidence? And how can insights coming from the study of groups of patients be used to inform the best care of individual patients? These questions influence the patient care that we provide.

The burden of potentially modifiable morbidity and mortality is greatest in the most poorly resourced countries of the world.[15] Most research emanates from upper income countries: it follows that the questions asked are those that are most relevant to those countries – whether it is the development of new approaches to treat disease, or the refinement of existing approaches through comparative effectiveness research. Common tropical diseases – dengue, malaria, melioidosis – receive less attention, and differences in disease patterns and in the organization and capacity of intensive care in LMICs mean that clinical approaches developed in upper income may not be effective in less-resourced settings.

Guidelines for the management of septic shock, for example, emphasize early and aggressive fluid resuscitation;[16] this approach to the treatment of childhood malaria in Kenya resulted in increased mortality.[17] A meta-analysis of studies of fluid resuscitation showed that outcomes differed between high and low and middle income countries,[18] likely a consequence of limited capacity to institute mechanical ventilation to manage the consequences of aggressive volume resuscitation.

The most important advances in the management of acutely ill patients have come not from the development of new drugs and devices, but from an improved understanding of how to optimize supportive care – to maximize its benefits while minimizing its harms.[19,20] Approaches to care vary because of variability in health care resources, health provider training, and local patterns of health care need. Research must reflect those local differences, and be designed and analyzed so that the impact of these differences on patient outcomes is adequately understood.

Research improves clinical care. It is the driving force behind a responsive and informed health care system. But efforts to build effective research programs in resource-limited settings face particular challenges.

Clinical Research: How

The barriers to clinical research in LMICs have been described by others,[14,21,22] and are summarized in Table 1. They fall into four broad categories.

1. Culture and Expectations

The concept that research must be a core element of the provision of clinical care, and integrated into the provision of that care, has only recently begun to be articulated. The dominant research model has been one whose primary focus is innovation, predicated in improving patient care through the introduction of new therapies rooted in the private sector. In the United States in 2018, for example, biopharmaceutical companies spent three times as much as the entire NIH budget – overs $100 billion - on research and development. Such an approach has a number of consequences. Clinical research is directed towards achieving regulatory approval and run by contract research organizations or a small number of academic research organizations with the needed expertise to negotiate the complex regulatory landscape. The resulting knowledge generated becomes intellectual property to be guarded to ensure a competitive advantage rather than to be shared. The role of health care workers in the conduct of research is tangential, and its relevance to ongoing care uncertain.

Table 1. Barriers to the conduct of clinical research in resource-limited settings.

Domain	Deficiencies & Challenges
Culture and Expectations	• Research environment • Role models • Awareness of research processes • Tradition of research • Concern that research implies lack of expertise
Resources	• Health care system support • Peer review funding • Dedicated research time; salary support • Competing time demands • Qualified research personnel
Administration and Logistics	• Ethical review processes • Contracts • Insurance and liability • Governmental processes
Collaboration and Mentorship	• Knowledge and technical skills • Leadership, role models • Peer support models such as trials groups

Clinician/investigator-driven research differs in that it addresses the questions that clinicians encounter in day-to-day practice. The model is particularly well developed in critical care medicine,[23] and has resulted in the development of national and regional critical care trials groups around the world,[24] including Brazil, Latin America, China, North Africa, and Southeast Asia. These groups have had a disproportionate impact on the clinical science of critical care,[25] and played a central role in evaluating treatments for COVID-19, both individually and through collaborations in platform trials such as the Randomized Embedded Multifactorial Adaptive Platform trial in Community-Acquired Pneumonia (REMAP-CAP) and the TOGETHER trial.[10,26-28] Beyond undertaking clinical research, groups of clinician-investigators are shifting the culture of and expectations for clinical research, building collaboration and collegiality,[8] and promoting the integration of research into clinical practice.[29]

The trials group model represents a potent tool for building research capacity in resource-limited areas. In Brazil, for example, the Brazilian Research in Intensive Care Network (BRICNet) has evolved from a fledgling group of clinician-investigators to a powerhouse network that has engaged hundreds of Brazilian intensive care units, and conducted landmark trials in intensive care.[30,31] The Latin American Intensive Care network (LIVEN) in South America conducted the ANDROMEDA Shock trial, showing the value of capillary refill assessment in targeting fluid resuscitation.[32]

Yet while trials groups can change the local culture of clinical research, initiatives by governments to embed research into practice can be much more influential. In 2006, the United Kingdom created the National Institute for Health Research (NIHR) to "create a health research system… which supports outstanding individuals, working in world-class facilities, conducting leading-edge research, focused on the needs of patients and the public".[33] The body mandated research in UK hospitals, providing financial support for research staff, establishing a prioritization process, and monitoring trial recruitment as a measure of the quality of care. As a consequence, the UK led the world in clinical research during the COVID-19 pandemic, recruiting nearly 50,000 patients to the RECOVERY trial, and guiding clinical care through rapidly emerging science. Indeed, the first report from RECOVERY – on the survival benefit provided by corticosteroids in severe COVID-19 – emerged a mere three months after the trial launch.[34]

These experiences can provide a roadmap for accelerating research in under-resourced areas, but additional barriers need to be overcome.

2. Resources

Research is expensive and time-consuming. Clinical trials to evaluate treatment options in the ICU environment typically require sample sizes of thousands of patients to generate reliable estimates of treatment efficacy. Were these run by the pharmaceutical industry, they would typically cost in excess of $50 million USD to conduct.[35] Investigator-led trials are less expensive, but still have budgets measured in millions of dollars.

Government funding for biomedical research is grossly inequitable, with upper income countries spending almost 30 times the amount spent in low-income countries, when evaluated as a percentage of the national GDP (Figure 2).[36] Private foundations such as the Wellcome Trust and the Bill and Melinda Gates Foundation provide support for research in LMICs, but the amounts fall far short of correcting an inequitable distribution of health research dollars.

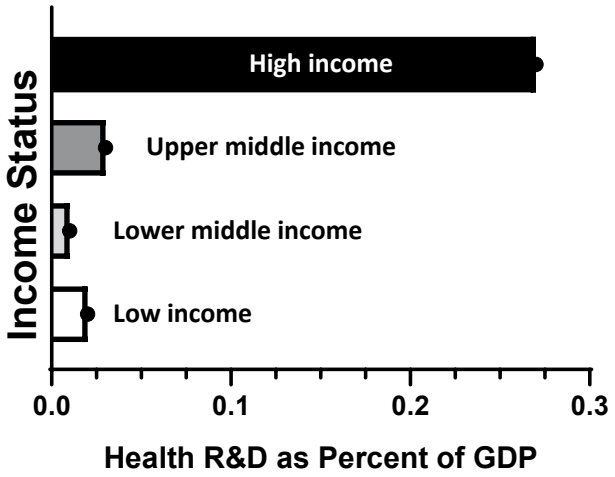

Fig. 2. *National Expenditure on Health Research and Development as a Percentage of Gross Domestic Product.*[36]

Research costs can be reduced by capturing data directly from electronic health records or from pre-existing registries.[37] Recruitment to the REMAP-CAP platform trial in Southeast Asia was facilitated by embedding data collection within the Critical Care for Asia and Africa (CCAA) registry.[38] Critical care registries with strong LMIC involvement such as the ISARIC registry or the LOGIC platform provide additional opportunities for enabling data collection.[39,40]

Providing clinicians with protected time for research has been a significant barrier. A variety of strategies in upper income countries address this need – group practice plans with income-sharing arrangements, endowed academic chairs, salary support grants from funding agencies, etc – and all leverage the reality that physician reimbursement for clinical work is generous. Salaries for research coordinators may be provided by the base institution, but commonly are supported or augmented by funds from running multiple clinical trials.

Expanding clinical research capacity necessitates a human resources strategy to ensure the availability of qualified investigators to conduct the work. Optimal models are likely to vary from country to country.

3. Administrative and Logistical Barriers

Multiple logistical and administrative challenges impede the greater integration of research into clinical care. Ethical review processes vary widely,[41] as do approaches to contracts, insurance, sponsorship, and other legal aspects of trial conduct. Addressing these barriers will require concerted efforts by policy-makers at the national and international level. The World Health Organization has called for the development of a maturity framework for the global clinical trials ecosystem as one element to harmonize and simplify approaches while maintaining alignment with principles of good clinical practice.[7]

4. Collaboration and Mentorship

Perhaps the greatest need, and the most immediate opportunity in building clinical trial capacity in resource-limited settings is to enhance international collaboration and leverage the experience of established research networks. Acquiring skill and confidence in research is an incremental process. Engaging in observational studies and registries provides an introduction to both research processes and research groups. Joining a multinational trial as a recruiting site adds to this experience, and sets the stage for designing and conducting research independently.

Clinical trials networks organized and led by active clinicians have proven to be superb venues for the education and mentoring of clinical researchers.[23] They have also become a mechanism to build international collaboration as trials to answer questions important to clinicians come to require sample sizes in the thousands. Recent, practice-changing clinical trials on the timing of initiation of renal replacement therapy,[42] the use of stress ulcer prophylaxis,[43] or the use of corticosteroids in patients with shock exemplify the trend towards greater international collaboration across research networks, a trend that has accelerated during the pandemic.[44] The Mega-ROX program evaluating oxygenation targets in mechanically ventilated patients has already recruited 25,000 (of a planned total of 40,000) patients into an international registry-based trial.[45] Collaboration increases the statistical power and generalizability of trial results, and is critical to the evolution of an acute care research ecosystem that grounds care in continuously updated knowledge derived through clinical trials. But until there is greater engagement of groups and sites in LMICs, the results of this effort will not necessarily improve the management of the most vulnerable patients in LMICs.

Networks of networks can support the dissemination of research capability to those areas where it is under-developed. The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC), a network of networks that study emerging infectious diseases (https://isaric.org/), is creating regional hubs in low and middle income countries to expand local capacity. The International Forum for Acute Care Trialists (InFACT), a global network of independent acute care research groups (https://www.infactglobal.org/), has held workshops to support emerging networks in Latin America, Africa, and Southeast Asia. The challenges are enormous, but the sense of need emerging from the COVID-19 pandemic and the burgeoning appetite for truly global collaboration is strong.

An evolving initiative of the World Health Organization can further support the global expansion of clinical research capacity. Patients with severe COVID-19 were typically hypoxemic. The optimal approach to their ventilator support was poorly characterized, although data from clinical trials did suggest that awake prone positioning could reduce the

frequency of intubation and that targeting a lower oxygen threshold could increase the number of days alive and free of organ support.[46,47] The need to understand the optimal support of hypoxemic patients is not unique to COVID-19, and supplemental oxygen is a scarce resource in LMICs.[48] The WHO is developing a globally federated clinical research program to address multiple aspects of the optimal provision of oxygen to hypoxemic patients, with a particular emphasis on the needs of LMICs.[49] The program has attracted the support of researchers and research networks around the world, and holds the promise of a further quantum step forward in building global research equity.

CONCLUSIONS

High quality health care is vitally dependent on reliable evidence deriving from clinical research, and delivered by expert clinicians who understand that evidence and its limitations. The essence of expertise lies less in what one knows, than in what we know to be unknown. Research hones expertise by identifying and addressing the unknown. This is a dynamic and perpetual process: as we come to better know the world of disease and the options in treating it, we change that world and generate new questions. We must move beyond the expectation that it is enough to apply evidence derived by others to a model of practice-based science, in which the process of care continuously addresses uncertainty, improving that care as it does so. We must integrate research into clinical care.

Unprecedented levels of international collaboration arising from the urgent needs of the pandemic have shown that this aspiration can be achieved, and a number of countries have begun to look to the model of the NIHR in the United Kingdom as a template for the future. Nowhere is the need more urgent, nor the benefits more compelling, than in the low and middle income countries that are home to the majority of the world's population.

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