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The International Collaboration for Research methods Development in Oncology (CReDO) workshops – Shaping the future of global oncology research

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Abstract

Low and middle-income countries (LMICs) face a disproportionately high burden of cancer and cancer mortality. The unique barriers to optimum cancer care in these regions necessitate context-specific research. The conduct of research in LMICs has several challenges, not least of which is lack of formal training in research methods. Building capacity by training early career researchers is essential to improve research output and cancer outcomes in LMICs.

The International Collaboration for Research methods Development in Oncology (CReDO) workshop is an initiative by the Tata Memorial Centre and the National Cancer Grid of India to address gaps in research training and increase capacity in oncology research. Since 2015, there have been five CReDO workshops, which have trained more than 250 oncologists from India and other countries in clinical research methods and protocol development. Participants from all oncology and allied fields were represented at these workshops. Protocols developed included clinical trials, comparative effectiveness studies, health services research, and observational studies, and many of them were particularly relevant to cancer management in LMICs. A follow-up of these participants in 2020 elicited an 88% response rate and showed that 42% of participants had made progress with their CReDO protocols, while 73% had initiated other research protocols and published papers.

In this policy review, we describe the challenges to research in LMICs, as well as the evolution, structure and impact of CReDO and other similar workshops on global oncology research.

Background

GLOBOCAN data suggest that the global cancer burden is increasing and is likely to be borne disproportionately by low and middle-income countries (LMICs).¹ By 2040, there will be a projected 29.5 million new cancer diagnoses and 16.5 million cancer-related deaths annually, with more than 75% of deaths likely to occur in LMICs.^{1,2} Data published by the Indian Council of Medical Research (ICMR) National Centre for Disease Informatics and Research (NCDIR) from the National Cancer Registry Program (NCRP) in India show that the absolute number of new patients with cancer annually has grown by 42% in the last decade.^{3,4} The mortality: incidence ratio is substantially higher in LMICs than high income countries (HICs) - 63% versus 38%.⁵ Some of these differences may be explained by overdiagnosis due to screening and detection of non-lethal cancers in HICs. However, they also reflect challenges to cancer management in LMICs such as delayed presentation, diagnosis at advanced stage, barriers to access and inability to afford treatment.^{6,7} These pose unique research questions which are specific to resource-constrained settings and are unlikely to be answered by research driven by or conducted in HICs.

A large proportion of oncology research in HICs is focused on systemic therapy including targeted therapy and immunotherapy with substantial costs but only marginal improvements in survival.^{8,9} The diffusion and adoption of major breakthroughs in modern cancer drugs is limited in LMICs, largely due to issues with affordability.¹⁰ For example, in a study from India, only 4% of eligible patients could afford trastuzumab as treatment for HER2 positive breast cancer.¹¹ LMICs are also poorly represented in genomic and sequencing studies, rendering the results of such studies minimally

relevant to them.¹² Moreover, areas of research focus in HICs do not reflect the disease burden in LMICs; half of cancer research in HICs is conducted on breast (18%), lung (14%), prostate (11%) and colorectal (7%) cancers, while cervix, head and neck, oesophago-gastric, and gall bladder cancers combined account for only 12%.¹³ Based on recent data from the ICMR-NCDIR-NCRP Investigators Group, the common cancers in India are lung, oral cavity, oesophagus and stomach in males and breast, cervix and ovarian cancers in females¹⁴; amongst these, only lung, breast and ovarian cancers are extensively researched in HICs. It has been estimated that hardly 2.7% of global cancer research investment is directly relevant to LMICs and that the results of many global oncology trials may not be generalisable to low-resource settings.^{14,15} There is a need to undertake context-specific research in LMICs which will address cancers and unique problems relevant to the region and develop implementable strategies to prevent, diagnose and treat cancer.

Healthcare research undertaken in LMICs is a small proportion of overall global research output. A review of Cochrane evidence on non-communicable diseases found that almost 90% of trials and 80% of research participants were from HICs.¹⁶ While India has approximately 17% of the world's population, it is involved in less than 2% of global clinical trials.¹⁷ Notably, oncology research output from LMICs is very low even for prevalent cancers such as cervical and oral cancer and for essential cancer management modalities like radiation therapy and palliative care.¹⁸⁻²¹ Randomised trials in oncology are dominated by authors from HICs, even though trials from LMICs were more likely to demonstrate the hypothesized difference in treatment outcome and were associated with larger effect sizes.²² For example, in 2012, Latin America accounted for

only 4% of cancer clinical trials in the world.²³ Although it is the second most populous country in the world, between 2012 and 2017, India ranked 18th in cancer research publications, contributing to just about 2% of global output.²⁴ Within India, there are large regional disparities in cancer research output, with research activities largely confined to a few large academic centres.²⁵ The major reasons for this low research output in LMICs include: lack of protected time and incentives for conducting research amidst heavy clinical care demands, lack of research infrastructure and support, limited domestic funding opportunities, inadequate understanding of trial methodology and regulations, insufficient training on research methods, lack of exposure to high-quality clinical and translational research and inexperience with the complexities of grant applications.^{26–32} Some of these problems (for example, lack of protected time and research infrastructure) require systemic solutions at a policy level and often reflect lack of institutional prioritisation of research as an independent endeavour worth pursuing. A few institutions like the Tata Memorial Centre have provided incentives to undertake practice-changing clinical research, develop clinician-scientists with Masters (Translational Research) training and conduct regular courses on basic clinical research methods.³³ These were supported by the creation of the Clinical Research Secretariat (CRS) and the Department of Atomic Energy Clinical Trials Centre (DAE-CTC) which provided support to clinician-researchers with research funding and biostatistics facilities, and created human resource by training clinicians and research coordinators. These strategies have resulted in landmark trials that have changed the management of several common cancers and scaling up at the national level through the National Cancer Grid of India (NCG) and the International Collaboration for Research methods

Development in Oncology (CReDO) initiative.³⁴⁻⁴⁰ However, these efforts also require a concerted effort to create learning opportunities for busy clinicians and allied healthcare workers without disrupting their clinical care demands.

The evolution of protocol development workshops in oncology

The global need for capacity building in oncology research was acknowledged in the 1990s, when it was recognized that there was a lack of expertise needed to design and conduct clinical trials. The Methods in Clinical Cancer Research Workshop (the Vail MCCR workshop), organised by the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) was developed in response to this need, with the first workshop held in 1996. Soon, the concept was replicated in Europe with the Methods in Clinical Cancer Research (Europe MCCR) Workshop organised by the European Organisation of Research and Treatment of Cancer (EORTC), European Society for Medical Oncology (ESMO), ASCO and AACR initiated in 1999 and in Australia with the Australia and Asia-Pacific Clinical Oncology Research Development (ACORD) Protocol Development Workshop first run in 2004. These workshops have trained approximately 250 oncologists (combined) annually. They have a stringent selection process, are over-subscribed, have non-negligible participation costs, prioritise participation from local regions, emphasise pharmaceutical-driven phase I and II trials evaluating new and expensive therapies, and hence are dominated by the types of oncology research undertaken in HICs. For example, around 58% of applicants were accepted to European MCCR workshop in the years 1999 to 2019 but acceptance was less than 30% for applicants from Central Asia. The Vail MCCR workshop has accepted between 35 and 50% of applicants in the last 5 years with most

participants from the United States. The ACORD workshop accepts approximately 50% of applicants, but is more diverse with participation from countries throughout the Asia Pacific with 40-50% of participants based outside Australia and New Zealand. Although participants from LMICs have the opportunity to participate in some of these workshops, the highly competitive selection process and logistics of travel and stay (despite the availability of grants) are deterrents to many. Additionally, the dominant focus of many of these workshops is novel therapeutics, which is much less important for cancer researchers in LMICs. Therefore, there was a clear unmet need for a similar workshop which could cater more specifically to the requirements of academic cancer researchers in LMICs.

The National Cancer Grid of India and the CReDO workshop

The National Cancer Grid (NCG) of India was established in 2012 by the Department of Atomic Energy, Government of India.³⁸ The mandate of the NCG is to establish uniform standards for prevention, diagnosis and treatment of cancer, provide specialised training and education in oncology, and facilitate collaborative basic, translational and clinical research in cancer. Currently, the NCG is a network of 226 cancer centres, research institutions, patient groups, professional societies and charitable organisations.³⁹ The NCG Secretariat is based at the Tata Memorial Centre (TMC), the largest tertiary-level cancer hospital in India. A key priority of the NCG has been to promote, support and prioritise innovative multi-centre research with emphasis on implementable solutions relevant to the management of cancers which are prevalent in or unique to the region. Some of the research-related initiatives of the NCG have been to facilitate the creation of research networks for specific cancers, the systematic

identification of gaps in current evidence, establishing an academic Contract Research Organization (CRO) and Clinical Trials Unit (CTU) and providing research funding as well as educational opportunities. The International Collaboration for Research methods Development in Oncology (CReDO) initiative was launched in 2015 by the NCG and the TMC with the objective of building research capacity in India by training early career faculty and trainees in various aspects of clinical research methods and to help participants convert research concepts into structured study protocols.⁴⁰ Notably, the CReDO workshop is the only one of the four oncology protocol development workshops conducted outside a HIC location.

The CReDO oncology research protocol development workshops

The first CReDO workshop was held in November 2015 followed by March 2017 and annually since then. The workshop is an intensive residential six-day course with a variety of learning activities including didactic talks, protocol development sessions, focused group discussions and faculty office hours. Applicants submit their curriculum vitae and career goals together with a short description of a clinical research project that they wish to develop. The highlight of the workshop is the daily protocol development break-out session where participants and faculty are divided into smaller groups for the purpose of developing specific elements of the individual protocols.. These groups are characterized by their high faculty: participant ratio (usually 4 faculty to 8 participants) which permit detailed discussions of the protocols being developed, allowing each participant to contribute to, and learn from the development of all the eight protocols in the group. These groups are deliberately kept small to facilitate active interactions between the participants and the faculty to understand the nuances of each component.

These sessions allow each participant to build various sections of the protocol on their own every day; the faculty members then review them and discuss the advantages and disadvantages of alternative designs, methods, conduct and analysis plans.

The CReDO organising committee recognised that conventional medical training necessarily focusses on good clinical skills. Research, however, requires specialised skills in study design, data aggregation and analysis. Didactic talks cover diverse topics in research methods including principles of writing a protocol, different study designs and their application, research ethics, grant writing, critical appraisal and manuscript writing. There is also substantial emphasis on biostatistics, which is an area of weakness for many participants. To facilitate protocol development discussions, the didactic talks on a particular day are carefully scheduled to aid participants according to the stage of the protocol they are likely to develop on that day. The direct one-on-one (faculty-hours) sessions between workshop participants and faculty experts allow detailed conversations to help clarify specific problems with individual protocols as well as career guidance and advice on other aspects of research. The focused group discussions allow in-depth discussions on specific topics which are key to certain research protocols – some of these include health economics, quality of life research, and novel trial designs. The faculty hours and focused group sessions provide participants with the opportunity to interact with faculty from outside their own protocol development groups and gain from the diverse experience, knowledge and skills of the faculty. The workshop is intense, with ten hours of scheduled activities each day, following which participants write up the relevant parts of their protocol and submit it to faculty, who send feedback overnight. Over the duration of the workshop, the research

concept outline is developed into a complete protocol which is robust and feasible and in a form which could be submitted to potential grant funders or ethics committees.

Entry into the workshop is open to anyone who is trained or training in oncology or a related field. Preference is given to early-career and mid-career oncologists who demonstrate commitment to continuing research in an academic setting. The application process is online and highly competitive, with each application reviewed by national and international experts for consideration of acceptance into the workshop. Applications are rated based on the novelty and relevance of the research idea (with particular emphasis on research questions that are relevant locally/regionally and are feasible to implement), the strength of the applicant's statement of purpose, recommendation from their mentor and potential added value that the applicant will bring to the institute by participating in the workshop.

The entry fee for the CReDO workshop is heavily subsidised (approximately 90% subsidy) and kept to a minimum (200 USD for participants from LMICs) to encourage applicants from all strata. The fee covers workshop registration, access to all workshop resources, local transportation, food and accommodation. In addition, we have been able to offer travel grants for many participants. This has been possible without industry support, due to generous funding from our supporting organisations which include the Tata Trusts, the US National Cancer Institute, the NCG, King's College London, ASCO, Cancer Research UK, and the ICMR.

CReDO participants and protocols: Between 2015 and 2020, we accepted 257 participants from a total of 667 applicants (38% acceptance rate). As part of the strategy to build oncology research capacity, eight applicants from various centres within the

NCG have attended the workshop as observers. In addition, we had seven biostatisticians from academic NCG centres participating in the workshops as part of a targeted effort to build capacity in clinical research statistics in the region. An objective of CReDO has been to encourage participation from diverse backgrounds and the selection process ensures fair representation from all regions with special emphasis on less developed areas with a higher cancer burden. So far, oncologists from more than 52 different cancer centres across India have attended the workshop. We have also had international participants from Tanzania, Zambia, Sri Lanka, Nepal, and Bahrain and from some HICs including Canada and the United Kingdom.

The emphasis of the Vail MCCR and the Europe MCCR workshops is on new drug development, with the majority of participants being medical oncologists; the ACORD workshop has a more diverse representation of oncological disciplines including nursing and allied health (Table 1). In contrast, a large proportion of the participants at the CReDO workshops are trainees or recent graduates in surgery and radiotherapy. Even among the pharmaceutical-based research projects at CReDO, the focus has been on drug repurposing rather than developing new drugs, especially using low cost and/or indigenous compounds such as curcumin, metformin, zinc, losartan and metronomic therapies. Several participants belong to allied specialties including epidemiology and public health, pathology, imaging, anaesthesiology, critical care, physiotherapy and palliative care (Table-1). The diversity of the research protocols developed at CReDO reflects the varied expertise and interests of participants, with ideas for low-cost surgical devices or interventions, development of indigenous technology, optimisation of existing resources, neoadjuvant therapy for downstaging tumours, de-intensified radiotherapy

regimens, cancer epidemiology and screening, and cost-effective techniques for diagnosis and follow-up. Qualitative and implementation research studies dealing with issues specific to LMICs such as challenges to accessing cancer care, barriers to opioid therapy, financial burden of cancer, issues related to abandonment of care and cultural validation of quality of life questionnaires have been designed at CReDO (Table-2). Research protocols developed at CReDO in the last 5 years have predominantly focused on cancers which are prevalent in LMICs – oral (20%), adult haematological (15%), breast (10%) cervical (7%) and paediatric (6%) cancers.

CReDO faculty: The faculty at the CReDO workshop are experienced researchers, trialists and statisticians from several countries; many of them have worked in other similar workshops and bring the advantage of that experience to CReDO. Mid-career oncologists from Indian centres, who have the potential to mentor junior colleagues at their institutes are also invited as faculty to CReDO, thereby building sustained mentorship in their respective institutions.

Impact of the workshop: Assessing the impact of a workshop is crucial to providing feedback into the content and structure of the sessions. To evaluate the immediate impact, each CReDO workshop has a pre- and post-test administered to participants, based on the workshop curriculum and comprising questions related to research study designs, research methods (including protocol writing) and biostatistics. The results of the test surveys have shown consistent improvements in participants' knowledge during the workshop. Over 5 editions of the workshop, the average relative increase in correct response rate between pre- and post-tests was 17% for biostatistics (range 6 to 28%), 14% for study designs (11 to 18%) and 10% for research methods (5 to 13%) We also

conduct periodic follow-up surveys of CReDO participants to assess the status of their research protocols and their overall research careers after CReDO participation. As of November 2020, 226 of 257 participants had responded to the survey (88% response rate); this is the most robust follow-up among all the oncology research methods workshops. Among those participants who attended between 2015 and 2019, 42% had made progress with their CReDO study protocols, more than 70% had worked on other protocols and many had received grants, and published research papers (Table-3).⁴¹⁻⁴⁶ In addition, the inter-participant and faculty-participant interactions during the workshops resulted in new collaborations leading to impactful publications.⁴⁷⁻⁵⁰

Evolution of the workshop: CReDO has evolved over the years, based on feedback from participants and faculty. The health education system in India, as in many other LMICs, does not lay much emphasis on research skills training as part of the medical training curriculum. Thus, unlike their counterparts in HICs, early and even mid-career researchers in India often have limited expertise with research methods, which could potentially limit their ability to engage and learn from the workshop. This was highlighted in the feedback from participants at the initial CReDO workshops. To address these deficits and ensure that participants enter the workshop with a certain baseline knowledge, we introduced a series of pre-workshop online sessions where, over a period of four months prior to the workshop, candidates selected for the workshop are exposed to key components of protocol development such as literature search, framing a research question, writing a protocol, basic statistics and research ethics.

Lack of research statistical support is a major challenge in many LMICs. The workshop programme has been tweaked to include several sessions on statistics to train

participants to analyse and interpret research data. Simultaneously, to build institutional capacity, statisticians from academic oncology centres within the NCG are invited to attend the workshop and gain from their interactions with the faculty. To encourage participants to sustain their research goals even after the workshop, we set up a system of post-workshop online webinars.⁵¹ These monthly sessions are a forum for continued teaching and act as a platform for discussions and problem-solving.

Lack of research funding has been cited as the main reason for non-progress of protocols developed at CReDO. Since 2016, the NCG has been funding multi-centre collaborative research on cancers which are prevalent or unique to the region. Researchers from institutes within the NCG who wish to apply for funding are encouraged to develop their ideas at the CReDO workshop. At our last 3 workshops, the best 7 protocols chosen by the CReDO workshop faculty each year were fast-tracked for consideration for NCG funding. Currently, the NCG is funding 11 academic trials, of which three were developed at the CReDO workshops.^{52,53} The results of these trials will fill knowledge gaps in the management of these cancers that occur commonly in India.

Future plans:

CReDO has increased its intake of participants from 40 in 2015 to 64 in 2020; however, this still represents just a third of applicants to the workshop. A priority for future workshops will be to expand capacity to allow more oncologists to benefit. However, there is always a balance between increasing numbers and providing the required level of individual attention and person-specific support. Participants from other low resource settings (including Sub-Saharan Africa and Sri Lanka) have shown an interest in

launching versions of the CReDO workshop in their own countries, which will serve to increase trained manpower for cancer research in LMICs. Lack of research support and infrastructure is an important challenge faced by many oncology centres in LMICs. The NCG has set up a CRO that supports member centres with the initiation, conduct and monitoring of investigator-initiated trials. We have also initiated an NCG network of cancer clinical trials sites across the country; this network will help establish collaborative research groups whose projects can be developed at future CReDO workshops. In addition, we are establishing the NCG CTU to assist academic investigators in key areas such as protocol development, statistical support and database management.

Discussion:

Cancer is a common cause of catastrophic health expenditure in LMICs.⁵⁴ The primary challenges related to the management of cancer in LMICs are access and affordability of care.^{6,7} Research in these settings should focus on developing population and hospital based cancer registries, tobacco control initiatives, identification of low-cost accessible techniques for screening, early diagnosis, treatment and palliation, development of resource-stratified guidelines and health systems research.^{55,56} In the context of limited research infrastructure and funding , good-quality observational studies (epidemiological data and cohort studies) should be encouraged as an adjunct to large pragmatic randomised trials to generate results which can inform policy and practice.

Given that clinical research from HICs is increasingly focused on developing highly personalised and expensive treatments, there is an opportunity for LMICs to focus their

clinical research on affordable treatments that can benefit large patient populations.¹⁰

There are several examples of academic studies from LMICs evaluating low-cost strategies which have produced practice-changing results globally. Some of these include the use of arsenic to improve outcomes in metastatic liver cancer, acetic acid for visual inspection for cervical cancer screening, evaluation of the need for neck node dissection in oral cancers, the use of a single depot-dose of hydroxyprogesterone to improve survival in breast cancer and the futility of local treatment in denovo metastatic breast cancer.^{34–37,57} It is important to note that financial toxicity and poor access is not limited to LMICs and occurs in HICs such as USA. Thus, research relevant to LMICs can have global application.

Recognizing the limitations of conducting research in resource-constrained environments, the CReDO workshop has consciously adapted to suit local priorities, setting it apart from other similar workshops. Some of the research proposals developed at the CReDO workshops are currently ongoing as large multicentric potentially practice-changing studies; these include, amongst several others, a randomised evaluation of the role of curcumin and metformin in preventing second primary tumours in patients with head and neck cancers (sample size 1500), a phase 3 randomised trial of postoperative radiotherapy in moderate risk oral cancers (sample size 392), and a treatment protocol for children and adolescents with relapsed acute lymphoblastic leukaemia (sample size 220) all of which are important clinical questions in LMICs.^{51,52,58}

The impact of research methods workshops such as CReDO extends far beyond the mere implementation of research protocols developed at the workshops. In addition to

training oncologists to carry out good-quality research, these workshops help participants to understand how to appraise literature and use evidence-based medicine to guide their clinical practice. Data from a long-term follow up evaluation of 235 applicants (167 participants and 68 applicants who had been rejected) at the Europe MCCR workshop showed that those who participated were more likely to develop other protocols and to have subsequent leadership roles. Similarly, in a one year follow-up survey of 500 participants at the Vail MCCR workshops, 57% showed progress with their workshop trial but more than 80% had worked on other research protocols and publications. Participants of a similar protocol development workshop in supportive oncology also reported extended impact of the workshop on their overall research careers.⁵⁹

As part of its global action plan to control non-communicable diseases, the WHO has emphasised the importance of strengthening research capacity to increase the ability of individuals and institutions to undertake good quality research and to engage with the wider community of stakeholders.⁶⁰ At the participant level, the CReDO workshop is creating a cadre of oncologists who can engage in academic research to provide robust results that impact health care decisions and policy. At the institutional level, the workshop helps to establish a pool of trained researchers and biostatisticians who can provide research support and mentor other oncologists. At the national and global level, the workshop promotes collaborative multi-centric research to identify solutions to regionally relevant questions. The impact of workshops such as CReDO highlights the need to create similar training opportunities in other parts of the world to increase contextually relevant research.

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References

1. Ferlay J, Ervik M, Lam F, et al. (2018). Global Cancer Observatory: Cancer Tomorrow. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.fr/tomorrow>, accessed [08 Dec 2020].
2. The Lancet. GLOBOCAN 2018: counting the toll of cancer. *Lancet*. 2018; **392**: 985.
3. Takiar R, Nadayil D, Nandakumar A. Projections of number of cancer cases in India (2010-2020) by cancer groups. *Asian Pac J Cancer Prev*. 2010; **11**: 1045–9.
4. Mathur P, Sathishkumar, Chaturvedi M. Cancer statistics, 2020. Report from the National Cancer Registry Programme, India. *JCO J Glo Oncol*. 2020; **6**: 1063–75
5. Ferlay J, Ervik M, Lam F, et al. (2018). Global Cancer Observatory: Cancer Tomorrow. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.fr/today/fact-sheets-populations>, accessed [08 Dec 2020]
6. Goss PE, Lee BL, Badovinac-Crnjevic T, et al. Planning cancer control in Latin America and the Caribbean. *Lancet Oncol*. 2013; **14**: 391–436.
7. Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, et al. Challenges to effective cancer control in China, India, and Russia. *Lancet Oncol*. 2014; **15**: 489–538
8. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics-the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg* 2014; **140**: 1225–36.
9. Prasad V, De Jesus K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol*. 2017; **14**: 381–90.
10. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. *N Engl J Med*. 2020; **328**: 674–8.
11. Ghosh J, Gupta S, Desai S, et al. Estrogen, progesterone and HER2 receptor expression in breast tumors of patients, and their usage of HER2-targeted therapy, in a tertiary care centre in India. *Indian J Cancer*. 2011; **48**: 391–6.
12. Drake TM, Knight SR, Harrison EM, Søreide K. Global Inequities in Precision Medicine and Molecular Cancer Research. *Front Oncol*. 2018; **8**: 346.
13. Seruga B, Hertz PC, Le LW, Tannock IF. Global drug development in cancer: a cross-sectional study of clinical trial registries. *Ann Oncol*. 2010; **21**: 895–900.
14. Sullivan R, Purushotham AD. Avoiding the zero sum game in global cancer policy: beyond 2011 UN high level summit. *Eur J Cancer*. 2011; **47**: 2375–80.

15. Wong JC, Fernandes KA, Amin S, Lwin Z, Krzyzanowska MK. Involvement of low- and middle-income countries in randomized controlled trial publications in oncology. *Global Health*. 2014; **10**: 83.
16. Heneghan C, Blacklock C, Perera R, et al. Evidence for non-communicable diseases: analysis of Cochrane reviews and randomised trials by World Bank classification. *BMJ Open*. 2013; **3**: e003298.
17. Saini KS, Agarwal G, Jagannathan R, et al. Challenges in launching multinational oncology clinical trials in India. *South Asian J Cancer*. 2013; **2**: 44–49.
18. Grover S, Xu M, Jhingran A, Mahantshetty U, Chuang L, Small W Jr, Gaffney D. Clinical trials in low and middle-income countries - Successes and challenges. *Gynecol Oncol Rep*. 2016; **19**: 5–9.
19. Sun GH, Houlton JJ, Moloci NM, MacEachern MP, Bradford CR, Prince ME, Jagsi R. Prospective head and neck cancer research: a four-decade bibliometric perspective. *Oncologist*. 2013; **18**: 584–91.
20. Pastrana T, Vallath N, Mastrojohn J, Namukwaya E, Kumar S, Radbruch L, Clark D. Disparities in the contribution of low- and middle-income countries to palliative care research. *J Pain Symptom Manage*. 2010; **39**: 54–68.
21. Aggarwal A, Lewison G, Rodin D, Zietman A, Sullivan R, Lievens Y. Radiation Therapy Research: A Global Analysis 2001-2015. *Int J Radiat Oncol Biol Phys*. 2018; **101**: 767–78.
22. Wells C, Sharma S, Del Paggio JC, et al. Global perspectives on clinical cancer research: A comparison of randomized controlled trial (RCT) design and outcomes across high income and low-middle income countries. *JAMA Oncology*. 2021 [Article in press]
23. Rolfo C, Caglevic C, Bretel D, et al. Cancer clinical research in Latin America: current situation and opportunities. Expert opinion from the first ESMO workshop on clinical trials, Lima, 2015. *ESMO Open*. 2016; **1**: e000055.
24. Cabral BP, da Graça Derengowski Fonseca M, Mota FB. The recent landscape of cancer research worldwide: a bibliometric and network analysis. *Oncotarget*. 2018; **9**: 30474–84.
25. Sullivan R, Badwe RA, Rath GK, et al. Cancer research in India: national priorities, global results. *Lancet Oncol*. 2014; **15**: e213–22.
26. Fundytus A, Sullivan R, Vanderpuye V, et al. Delivery of Global Cancer Care: An International Study of Medical Oncology Workload. *J Glob Oncol*. 2018; **4**: 1–11.

27. Seruga B, Sadikov A, Cazap EL, et al. Barriers and challenges to global clinical cancer research. *Oncologist*. 2014; **19**: 61-7.
28. Dandekar M, Trivedi R, Irawati N, Prabhash K, Gupta S, Agarwal JP, D'Cruz AK. Barriers in conducting clinical trials in oncology in the developing world: A cross-sectional survey of oncologists. *Indian J Cancer*. 2016; **53**: 174–7.
29. Rubagumya F, Nyagabona SK, Msami KH, et al. Attitudes and Barriers to Research Among Oncology Trainees in East Africa. *Oncologist*. 2019; **24**: e864–9.
30. Bhatia RK, Sastri Chopra S, Palkonda VAR, et al. Assessing radiation oncology research needs in India: Results of a physician survey. *Indian J Cancer*. 2020; **57**: 457–62.
31. Schmutz A, Salignat C, Plotkina D, et al. Mapping the Global Cancer Research Funding Landscape. *JNCI Cancer Spectr*. 2019; **3**: pkz069.
32. Organisation for Economic Co-operation and Development. OECD recommendation on the governance of clinical trials (2013). [Internet]. Available from: <http://www.oecd.org/sti/inno/oecd-recommendation-governance-of-clinical-trials.pdf>, accessed [8 December 2020].
33. King's College London. Translational Cancer Medicine MRes. [Internet]. Available from: <https://www.kcl.ac.uk/study/postgraduate/taught-courses/translational-cancer-medicine-mres>, accessed [8 December 2020].
34. Shastri SS, Mittra I, Mishra GA, Gupta S, Dikshit R, Singh S, Badwe RA. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. *J Natl Cancer Inst*. 2014; **106**: dju009.
35. D'Cruz AK, Vaish R, Kapre N, et al; Head and Neck Disease Management Group. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. *N Engl J Med*. 2015; **373**: 521–9.
36. Badwe R, Hawaldar R, Parmar V, et al. Single-injection depot progesterone before surgery and survival in women with operable breast cancer: a randomized controlled trial. *J Clin Oncol*. 2011; **29**: 2845–51.
37. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol*. 2015; **16**: 1380–8.
38. Pramesh CS, Badwe RA, Sinha RK. The national cancer grid of India. *Indian J Med Paediatr Oncol*. 2014; **35**: 226–7.

39. Tata Memorial Centre. National Cancer Grid. [Internet]. Available from: <https://tmc.gov.in/ncg/>, accessed [9 December 2020].
40. Tata Memorial Centre. International Collaboration for Research methods Development in Oncology (CReDO) workshop. [Internet]. Available from <https://tmc.gov.in/credo/>, accessed [9 December 2020].
41. Bhandoria G, Mane JD. Can Surgical Apgar Score (SAS) Predict Postoperative Complications in Patients Undergoing Gynecologic Oncological Surgery? *Indian J Surg Oncol*. 2020; 11: 60–65.
42. Malik A, Nair S, Sonawane K, et al. Outcomes of a Telephone-Based Questionnaire for Follow-up of Patients Who Have Completed Curative-Intent Treatment for Oral Cancers. *JAMA Otolaryngol Head Neck Surg*. 2020: e202404. (Epub ahead of print).
43. Engineer R, Patkar S, Lewis SC, et al. A phase III randomised clinical trial of perioperative therapy (neoadjuvant chemotherapy versus chemoradiotherapy) in locally advanced gallbladder cancers (POLCAGB): study protocol. *BMJ Open*. 2019; **9**: e028147.
44. Agarwal R, Rajanbabu A, P V N 5th, Goel G, Madhusudanan L, U G U. A prospective study evaluating the impact of implementing the ERAS protocol on patients undergoing surgery for advanced ovarian cancer. *Int J Gynecol Cancer*. 2019; **29**: 605–12.
45. Hariharan N, Rao TS, Rajappa S et al. Accuracy of core biopsy in predicting pathologic complete response in the breast in patients with complete/near complete clinical and radiological response (Complete Responders in the Breast - CRBr) - Trial design and conduct. *Int J Surg Protoc*. 2019; **16**: 5–8.
46. India Alliance - Advancing Discovery and Innovation to Improve Health [Internet]. Available from: <https://www.indiaalliance.org/fellows>, accessed [08 Dec 2020]
47. Bhandoria G, Shylasree TS, Bhandarkar P, Ahuja V, Maheshwari A, Sekhon R, Somashekhar SP. Impact of COVID-19 Pandemic on Gynecological Oncology Care: Glimpse into Association of Gynecological Oncologists of India (AGOI) Perspective. *Indian J Gynecol Oncol*. 2020; **18**: 71.
48. Bhandoria GP, Bhandarkar P, Ahuja V, et al. Enhanced Recovery After Surgery (ERAS) in gynecologic oncology: an international survey of peri-operative practice. *Int J Gynecol Cancer*. 2020; **30**: 1471–8.
49. Cyriac S, Booth CM. Delivery of Cancer Care in India and Canada: Opportunities for Bidirectional Learning. *J Glob Oncol*. 2019; 5: 1–5.

50. Jha AK, Mithun S, Jaiswar V, et al. Repeatability and reproducibility study of radiomic features on a phantom and human cohort. *Sci Rep.* 2021;11:2055.
51. National Cancer Grid. CReDO research webinars [Internet]. Available from <https://tmc.gov.in/ncg/index.php/credo-research-talks>, accessed [08 Dec 2020]
52. Clinical Trials Registry India [Internet]. New Delhi: database publisher (India). 20 Jun 2007. Identifier CTRI/2017/07/009114, Adjuvant Radiotherapy in Early Stage Oral Tongue Cancers (AREST) – a prospective randomized control trial; 27 Jul 2017 [cited 08 Dec 2020]; [1 page]. Available from: <http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=16703&EncHid=&userName=CTRI/2017/07/009114>
53. Clinical Trials Registry India [Internet]. New Delhi: database publisher (India). 20 Jun 2007. Identifier CTRI/2018/03/012274, Phase IIb/III study to determine efficacy of Curcumin and Metformin to reduce the incidence of second primary tumors of aero-digestive tract in patients with history of head and neck squamous cell carcinoma; 01 Mar 2018 [cited 08 Dec 2020]; [1 page]. Available from: <http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=21431&EncHid=&userName=CTRI/2018/03/012274>
54. Gelband H, Sankaranarayanan R, Gauvreau CL, et al; Disease Control Priorities-3 Cancer Author Group. Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from Disease Control Priorities, 3rd edition. *Lancet.* 2016; **387**: 2133–44.
55. Sankaranarayanan R, Boffetta P. Research on cancer prevention, detection and management in low- and medium-income countries. *Ann Oncol.* 2010; **21**: 1935–43.
56. Kingham TP, Alatisse OI. Establishing translational and clinical cancer research collaborations between high- and low-income countries. *Ann Surg Oncol.* 2015; **22**: 741–6.
57. Wang HY, Zhang B, Zhou JN, et al. Arsenic trioxide inhibits liver cancer stem cells and metastasis by targeting SRF/MCM7 complex. *Cell Death Dis.* 2019; **10**: 453.
58. Clinical Trials Registry India [Internet]. New Delhi: database publisher (India). 20 Jun 2007. Identifier CTRI/2019/10/021758, The Indian Paediatric Oncology Group collaborative multicentre treatment protocol for children and adolescents with relapsed acute lymphoblastic leukaemia (InPOG ALL R1); 22 Oct 2019 [cited 08 Dec 2020]; [1 page]. Available from:

<http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=37122&EncHid=&userName=CTRI/2019/10/021758>

59. Pirl WF, Greer JA, Park E, et al. Development and evaluation of a six-day training program in supportive oncology research. *Palliat Support Care*. 2018; **16**: 656–61.
60. ESSENCE on Health Research. Seven principles for strengthening research capacity in low- and middle-income countries: simple ideas in a complex world. ESSENCE on Health Research, Geneva, Switzerland (2014) 31 pp. [ESSENCE Good practice document series. TDR/ESSENCE/2.14.]. Available from: <https://www.who.int/tdr/publications/seven-principles/en/>, accessed [08 Dec 2020]

Table-1: Specialty-wise distribution of participants at the various workshops

Specialty	CReDO (n=257) (2015, 2017, 2018, 2019, 2020)	Vail MCCR (n=500) (2015, 2016, 2017, 2018, 2019)	Europe MCCR (n=399) (2014, 2015, 2016, 2018, 2019)	ACORD (n=510) 2004, 2006, 2008, 2010, 2012, 2014, 2016, 2018
Surgical Oncology (including gynaec and uro-oncology)	91 (35%)	32 (6%)	38 (10%)	57 (11%)
Medical/ Hemat Oncology/ Paediatric Oncology	71 (28%)	391 (78%)	281 (70%)	332 (65%)
Radiation/Clinical Oncology	39 (15%)	63 (13%)	64 (16%)	46 (9%)
Allied specialties	56 (22%)	14 (3%)	16 (4%)	75 (15%)
<i>Palliative Care</i>	9		1	15
<i>Public Health</i>	8		0	
<i>Anaesthesiology/Critical Care</i>	7		0	
<i>Clinical Research</i>	6		0	
<i>Imaging/Nuclear Medicine</i>	5		8	
<i>Clinical Pharmacology</i>	4		0	6
<i>Pathology</i>	4		0	
<i>Psycho-Oncology</i>	3		0	6
<i>Translational Research</i>	3		0	
<i>Not specified / Others</i>	7	14	7	48

Table-2: Types of studies developed at CReDO

Type of research	Examples
Basic research	Molecular profiling of tumours, predictive and prognostic biomarkers
Epidemiology	Prevalence and risk factors for common cancers
Screening and diagnosis	Cost-effective screening and diagnostic methods for prevalent cancers such as oral, breast and cervical cancers
Drug repurposing	Use of low-cost and/or indigenous drugs like ciprofloxacin for prostate cancer, statins in rectal cancer, chloroquine for glioblastoma, curcumin and metformin in upper aerodigestive tract tumours, esomeprazole in osteosarcoma
Frugal innovation	Development of genetically modified E.Coli derived L-asparaginase, low-cost voice prosthesis costing 1 dollar
Low-cost or resource-sparing strategies	Nutritional interventions, health education, sleep hygiene, psychotherapy, yoga, physiotherapy, de-escalation of radiotherapy, less intensive follow-up regimes, cost-effective imaging techniques, modifications in surgical techniques, development of risk-based treatments
Outcomes research	Oncological outcomes, peri-operative complications, assessment of quality of life
Quality improvement	Awareness of disease, assessing information needs of patients and care-givers, reasons for abandonment of treatment, gender disparities, perceptions of meaningful benefit
Implementation research	Compliance with guidelines, barriers to accessing therapy
Health economics	Evaluation of the financial burden of cancer
Research on secondary data	Systematic reviews, development of risk scores, automated risk prediction tools

Table-3: Follow-up of CReDO participants

Attended between 2015 and 2019 (n=193) Responders (n=163)	
Status of CReDO project	
Completed/Published	14 (9%)
Ongoing	33 (20%)
Submitted to Institutional review board	22 (13%)
No progress	94 (58%)
If no progress, reasons (n=94)	
Moved to different institute	27
Lack of funds	19
Lack of institutional support	11
Idea no longer scientifically valid	7
Lack of time/motivation	3
Not specified/Others	27
Worked on other protocols after CReDO	118 (73%)
Published papers after CREDO	119 (73%)

Search strategy and selection criteria

This Policy Review was prepared by the organising committee (PR, GC, MS, DG, ST, RAB, CSP) of the International Collaboration for Research methods Development in Oncology (CReDO) workshop, which is organized by the Tata Memorial Centre (TMC), the largest cancer hospital in India and the National Cancer Grid of India (NCG), a network of 226 cancer centres, research institutions, patient groups, professional societies and charitable organizations across India. The additional authors are either faculty on the CReDO workshop (CMB, MB, CF, MK, RL, XP, MP, AP, P Rajaraman, MRS, RS and IT) or represent organisations which support the workshop (BB, SC, SG, NG, PM, DP, SS, ET). Some of the authors are also faculty on other similar workshops and helped to obtain data related to those workshops (MK – Vail MCCR workshop, XP – Europe MCCR workshop, MRS – ACORD workshop)

In preparation of the report, we searched the literature on PubMed using the terms “oncology research”, “research training”, “protocol development workshop” AND “research capacity” without applying a date range. Only papers published in English were considered. References were selected according to their relevance to the Policy Review. Annual reports and other follow-up data were obtained from the Europe MCCR, the Vail MCCR, and the ACORD workshops.

Authors' contributions

Priya Ranganathan, C S Pramesh - Concept, literature search, study design, data collection, data analysis, data interpretation, writing

Girish Chinnaswamy, Manju Sengar, Durga Gadgil, Shivakumar Thiagarajan, Douglas Pyle, Xavier Paoletti, Martin R. Stockler - Concept, data collection, data analysis, data interpretation, writing

Balram Bhargava, Prashant Mathur, Sanjiv Chopra, Satish Gopal, Nick Grant, Soumya Swaminathan, Edward Trimble - Concept, data interpretation, writing

Christopher M. Booth, Marc Buyse, Chris Frampton, Mark Krailo, Ruth Langley, Mahesh Parmar, Arnie Purushotham, Preetha Rajaraman, Richard Sullivan, Ian Tannock, Rajendra Badwe - Concept, study design, data interpretation, writing

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