Clinical Trials in Palliative Care: Need for Serious Reckoning

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ACCOMPANYING CONTENT

Appendix

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May 20 marked the International Day for Clinical Trials (CT), which prompted a few reflections on the landmark trials in palliative care.[1] James Lind's pioneering study aboard the HMS Salisbury illuminated scurvy's treatment, whereas Fletcher's trial at Kuala Lumpur Lunatic Asylum unveiled Beri-Beri's cause.[2,3] These milestones ushered in Evidence-Based Medicine (EBM) and shaped medical practice since its conception by Prof Guyaat at McMaster University.[4] These intertwined facets of scientific progress gradually reveal a comprehensive understanding.

Arguably, one may question the leaps that medical science has achieved in the past five to six decades, no major paradigm shifts, or Eureka discoveries but sustained efforts to generate evidence-based, scientifically robust treatment changes. These small raindrops of information have now resulted in a nourishing river of medical knowledge, which now aims to address problems universally. Clinical trials are the modern-day Sherpas trained to reach the summits of improved patient care, from disease screening to palliative care. A Randomized Clinical Trial (RCT) is by far the most powerful tool to change clinical practice.[5] However, using clinical trials as the holy grail has its limitations. Here, I would be discussing five major aspects of clinical trials relevant from the perspective of not just Palliative Medicine but Medicine at large (Appendix).

First, setting our priorities right is crucial. Addressing diverse motivations for clinical trials is crucial. Moving beyond disparate goals, pragmatic trials focusing on palliative care needs take precedence. From dead honest research questions arising from the clinics to extremely desperate pharma-/device industry–driven, from getting extended US Food and Drug Administration (FDA) approval to overly ambitious clinician-scientists finding a podium presentation or citation in the next *JCO*, *Lancet*, or *NEJM*, clinical trials have seen them all.[5,6] While course correction leads to a more mature thought process, ongoing discussions about setting the right end points in a clinical trial highlight the importance of overall survival benefit or quality-of-life (QoL) benefit over surrogates in oncology and palliative settings.[7] As rightly suggested by Wells et al,[8] we require more pragmatic trials focusing on palliative care needs rather than investigating pharma-funded palliative systemic therapies alone. In a study assessing the benefits of 118 FDA-approved oncologic indications, 105 clinical trials from 2006 to 2016 showed only a mere 43% meaningful benefit. Less than 40% of them studied overall survival and wayless, approximately only 15%, showed improved QoL.[9]

Second, the scandal of poor clinical trials (inspired by the famous Doug Altman's[10] 1994 *BMJ* paper) emphasizes the importance of avoiding poor starts. As clinicians, we tend to answer wonderful question in our clinical trials but lack in designing and implementing a good clinical trial. An eye-opening revelation was a study which showed that risk of bias in published trials from our domain of pain and palliative and supportive care is upward of 90%.[11] Chalmers and Glasziou[12] in the *Lancet* have reported that 85% of the research funding is wasted mainly because of poor clinical trial design and implementation. Methods—such as mandatory use of statistical expertise for both ethical and funding approvals, use of risk bias tools at the design level, making them multicentric all inclusive, establishing dedicated research secretariat for assistance and a very active data safety monitoring committee, and reserving funds for improvement in clinical trials—should help address this issue.[13,14]

Third, the issue of ethical funding needs attention. It is a bit of a cliché that any research needs more funding and palliative care research funding is neglected. Most of the health spending in low- and middle-income countries (LMICs) like India is not dedicated to research. The annual budget of Indian Council of Medical Research is $300 million US dollars which is <0.01% of

India's gross domestic product; Disney studios recently spent more than this on their new science fiction movie.[15,16] Global health funding should also prioritize CTs in LMICs as they generate better meaningful and value adding clinical trials than high-income countries.[17] In a review of 694 RCTs in oncology, it was found that a majority of them (65%) were in a palliative setting; however, approximately nine of 10 were to study a systemic therapy in these settings, and only 8% were led by LMICs.[8] As Professor Sullivan, the Director of the Institute of Cancer Policy, King's College, London, rightly puts it, "We must ramp up scholarly output to help support the healthcare communities who are on the front line of this crisis" to not only support LMICs with funding but also help publish their results globally.[18] Without dwelling into the vicious circle of pharma-funded trials and their conflicts of interest, there is hope in alternative, nonprofit groups such as Protas in the United Kingdom who were instrumental in conducting the famous RECOVERY trial in COVID-19 using novel funding methods to cite an example.[19] Funding also brings the question of how frugal we are when it comes to research budgeting. We need to be modest with our grant awards and avoid the use of academic privileges to usurp grants, and funding bias needs to be stopped. A more inclusive and pragmatic approach toward grants to early career researchers, institutes with limited access, and individuals working in hardship zones, where it may be difficult to get all the administrative support, must be encouraged.

Fourth, we need more Ground shots than Moonshots (as Prof Christopher Booth puts it) in CTs.[20] As palliative care physicians, we need to target many simple yet effective treatment strategies and provide more emphatic ways to find the solution and conduct CTs. These trials would then cost a fraction, would require minimal medical infrastructure, and would be implemented in low-resource settings, overcoming the usual barriers for conducting clinical trials. Palliative patients do not need new technology alone, they need more care, and focus should not be on a newer metered drug-dispensing device or a fancy nutrition supplement.[21,22] In LMICs and low-income countries, the use of mHealth has been proposed as a game changer; however, issues of scalability, language, sociocultural issues, and data privacy have made it just another means to siphon funds, with AI being projected as the space shuttle for this moonshot.[23] Effective repurposing of drugs and their dosing, opioid literacy, adaptive use of palliative care models at the community level, increasing the access to palliative care, and pragmatic trial designs making the patient as the center of focus would be effective solutions to these.[22-24]

Finally, we need more collaboration in clinical trials. What we require in medicine, in general, and palliative care, in particular, is the amalgamation of humanities, technology, artificial intelligence, and medicine.[25] Despite the mushrooming of multiple academic institutions and the increased funding in India, what is missing is the cross talk required for such good CTs. To foster integrative learning and research ideas, we as physicians should avoid the professional grandstanding as doctors and treat our nonmedical collaborators as equals, which would lead to actual improvement in our CTs. Shared intellectual proprietary and academic credit are essential for delivering high-quality CTs.

To conclude, I would like to quote the famous Oxford professor of Statistics in Medicine, Late Doug Altman "We need less research, better research, and research done for the right reasons."[10]

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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REFERENCES

1. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733-742, 2010
2. Lind J: The James Lind Library, 1753. https://www.jameslindlibrary.org/lind-j-1753/
3. Bhatt A: Evolution of clinical research: A history before and beyond James Lind. Perspect Clin Res 1:6-10, 2010
4. Smith R, Rennie D: Evidence-based medicine—An oral history. JAMA 311:365-367, 2014
5. Lang T, Siribaddana S: Clinical trials have gone global: Is this a good thing? PLoS Med 9:e1001228, 2012
6. Gyawali B, Sullivan R: Economics of cancer medicines: For whose benefit? New Bioeth 23:95-104, 2017

7. Gyawali B, Booth CM: Cancer treatments should benefit patients: A common-sense revolution in oncology. Nat Med 28:617-620, 2022
8. Wells JC, Sharma S, Del Paggio JC, et al: An analysis of contemporary oncology randomized clinical trials from low/middle-income vs high-income countries. JAMA Oncol 7:379-385, 2021
9. Tibau A, Molto C, Ocana A, et al: Magnitude of clinical benefit of cancer drugs approved by the US Food and Drug Administration. J Natl Cancer Inst 110:486-492, 2018
10. Altman DG: The scandal of poor medical research. BMJ 308:283, 1994
11. Pirosca S, Shiely F, Clarke M, et al: Tolerating bad health research: The continuing scandal. Trials 23:458, 2022
12. Chalmers I, Glasziou P: Avoidable waste in the production and reporting of research evidence. Lancet 374:86-89, 2009
13. Ioannidis JPA, Greenland S, Hlatky MA, et al: Increasing value and reducing waste in research design, conduct, and analysis. Lancet 383:166-175, 2014
14. Van Calster B, Wynants L, Riley RD, et al: Methodology over metrics: Current scientific standards are a disservice to patients and society. J Clin Epidemiol 138:219-226, 2021
15. Indian Council of Medical Research: Government of India. https://main.icmr.nic.in/
16. How Much Avatar 2 Cost and How Much it Needs to Make | Time. https://time.com/6241639/avatar-2-costs-box-office/
17. Alemayehu C, Mitchell G, Nikles J: Barriers for conducting clinical trials in developing countries- a systematic review. Int J Equity Health 17:37, 2018
18. ecancer Is Supporting Publications on Cancer Care in Lower and Middle Income Countries—ecancer. https://ecancer.org/en/news/18114-ecancer-is-supporting-publications-on-cancer-care-in-lower-and-middle-income-countries
19. Mahase E: Recovery trial lead launches organisation to cut costs of clinical trials. BMJ 376:o203, 2022
20. Gyawali B, Sullivan R, Booth CM: Cancer groundshot: Going global before going to the moon. Lancet Oncol 19:288-290, 2018
21. Sullivan R, Pramesh C, Booth C: Cancer patients need better care, not just more technology. Nature 549:325-328, 2017
22. Hasson F, Nicholson E, Muldrew D, et al: International palliative care research priorities: A systematic review. BMC Palliat Care 19:16, 2020
23. Mutebi M, Dehar N, Nogueira LM, et al: Cancer groundshot: Building a robust cancer control platform in addition to launching the cancer moonshot. Am Soc Clin Oncol Ed Book 42:1-16, 2022
24. HOME: National Cancer Grid of India. International Collaboration for Research Methods Development in Oncology (CReDO) Workshop. https://tmc.gov.in/credo/
25. Transcript for the Arts and Humanities in Medicine—AM Rounds. https://academicmedicineblog.org/transcript-for-the-arts-and-humanities-in-medicine/

APPENDIX. CONTEXT AND KEY OBSERVATION

International Clinical Trials Day (ICTD), observed annually on May 20, serves as a poignant backdrop for discussions on the significance of clinical trials (CTs) within the realm of palliative care. In the context of ICTD 2023, this discourse holds special relevance, prompting a focused exploration of how CTs contribute to informed decision making, enhanced patient care, and improved quality of life.

Amid the wealth of data at our disposal, it becomes evident that quality research and clinical trials are imperative, particularly within the field of Palliative Medicine and symptom care. This urgency stems from the growing recognition of the pivotal role that CTs play in addressing the unique challenges faced by patients in need of palliative care.

Key Observations

Setting Priorities: The first key area of focus centers on setting appropriate priorities. By aligning research goals with genuine clinical needs, CTs can yield outcomes that directly affect patient care.

Avoiding Poor Trials: The second observation revolves around the avoidance of subpar clinical trials. Highlighting the dire consequences of inadequately designed trials, this point underscores the necessity of methodological rigor.

Ethical Funding: The third area emphasizes the ethical dimension of funding. Given the prevailing funding disparities in palliative care research, this observation emphasizes the importance of equitable allocation of resources.

Ground Shots versus Moonshots: The fourth observation encourages a pragmatic approach in CTs, emphasizing ground shots—achievable and impactful strategies—over aspirational moonshots.

Collaborative Approach: The fifth and final observation underscores the power of collaboration. By weaving together diverse perspectives from fields such as humanities, technology, artificial intelligence, and medicine, CTs can reach new heights of inclusivity and effectiveness.