## Title
Control participants of randomised trials: an often forgotten, vulnerable population



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# Control participants of randomised trials: an often forgotten, vulnerable population

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A lot of attention is rightfully given to racial and socioeconomic disparities in cancer care.[1] It is certain that disadvantaged groups have less access to life-extending oncology care, with subsequent inferior outcomes observed consistently over the past five decades.[1] Unfortunately, addressing disparities has been slow, and there is evidence that for some cancers such as myeloma, recruitment of racial minorities in trials that can provide patients with potentially life-saving medications has not noticeably improved over the past decade.[2] These disparities are especially unfortunate for underrepresented minorities, because not only do patients lose their chance to receive potentially novel life-saving medications as part of a clinical trial, but the results of these trials might not be generalisable to those minorities.

There is another uniquely vulnerable population that does not receive much attention in oncology—patients that are enrolled in the control groups of clinical trials. Many safeguards have evolved to protect the rights of patients in clinical trials,[3] including federal oversight, local institutional review boards, and a vast amount of bureaucracy for this purpose. Nevertheless, it is now obvious that despite the best intention of these bodies, inferior control groups affect oncology clinical trials. Many approvals in oncology are based on trials ran with inferior control groups,[4] and many control groups are known to be inferior well before even enrolling the first patient.[5] Simply put, a participant assigned to a control group of these studies often receives worse care than what they would receive if they were treated off-protocol with the prevailing standard of care.

The current landscape of trial design leaves the conduct of modern randomised trials largely in the hands of the pharmaceutical industry.[6] Oncologists are faced with difficult choices; they might disagree with some aspects of the trial, such as an inferior control group, but are forced to accept them because some patients might benefit from being on the intervention group. This situation is particularly pronounced in low-income countries that do not have access to new therapies. Key physician leaders in academia serve as principal investigators and first authors but might not have much critical input in the design and choice of control groups. Public critique of the conduct of these trials might thus lend to physicians being seen as not willing to engage with the pharmaceutical industry, and many oncologists fear that this might lead to the trial not being available at their institutions, and patients losing access to options. Unfortunately, the same leaders who might advocate for better representation of minorities on trials are silent about the inferior care the vulnerable control population might receive in the trials they are leading.

Another often neglected aspect of trial equity is post-protocol therapy. Reporting of post-protocol therapies is sparse, and when reported, often is in a hard-to-find and poorly explained supplemental section.[7] Furthermore, details on post-protocol therapy can be onerous to collect and report. Across oncology trials, patients

in control groups often do not receive the proven, standard-of-care therapy after progression,[8] a tragic situation in which patients who have agreed to remain enrolled on a control group—despite the control group being inferior to standard of care—do not receive access to highly effective therapies that the sponsor could have provided.

The absence of adequate post-protocol therapy often stems from the fact that trials are frequently conducted in areas of the world where the prevailing standard of care is inferior to that of the USA or western Europe, probably due to reasons of cost and access. The intent is usually to gain approval in the USA and western Europe and hence, after the trial period is completed, patients in the control group of these trials are left without access to highly effective treatments that the trial sponsor might have provided in these countries.[9] Essentially, socioeconomic differences between countries are exploited, with low-income countries producing data that is used for and by high-income countries.

As an example, most patients who were assigned to the control group in recent trials of daratumumab for newly diagnosed multiple myeloma did not receive daratumumab upon progression, despite daratumumab being approved for use in the USA since 2015 and multiple trials having shown its efficacy in the relapsed or refractory setting.[7] This was largely because of the trials being ran in locations where daratumumab might not have been approved at the time of the study, and the sponsor not guaranteeing access to this drug after the trial period. Another example of global disparity being used to the sponsors advantage is the trial of selinexor–bortezomib–dexamethasone compared with bortezomib–dexamethasone for relapsed multiple myeloma.[10] This trial enrolled control participants well after it was known that bortezomib–dexamethasone was inferior to another doublet (carfilzomib–dexamethasone), let alone other three-drug regimens, such as daratumumab-based triplets or triplets incorporating carfilzomib or pomalidomide. The trial did not enrol many patients in the USA because the control regimen would not have been acceptable there, but instead enrolled patients in other countries, where better regimens might not have been widely available and affordable, and hence an inferior control group was considered more palatable by local investigators.[10]

Although we have recognised for a long time that socioeconomic and racial disparities exist in our society, efforts to address them are lagging and much needed. At the same time, addressing the inequalities that the vulnerable control participants face is also important—and lies immediately within the hands of the biomedical community. Let us all advocate for better control groups—provide the best globally available standard of care, guarantee adequate post-protocol therapy, and allow easier scientific discourse and communication on the often vastly inferior care these patients receive.

Current trial design is the result of a set of constraints: regulatory, those set by health technology assessment agencies, and obviously cost. Potential solutions include greater regulatory oversight from agencies such as the US Food and Drug Administration on the design of the control group for such trials. Archaic rules from regulatory agencies on what a control group is might not reflect the actual standard of care in practice, and greater flexibility from the regulatory agencies might serve patients well. Guarantees from the sponsor to provide adequate post-protocol therapy to the control group should be sought, and accountability held should there be failure to do so. If a therapy is known to be beneficial before trial enrolment, the sponsor should be mandated to provide that therapy—even if that therapy is not available at the country where the trial is running. Trial sponsors should work together with stakeholders in low-income and middle-income countries to not just ensure the study drug is available upon successful completion of the clinical trial but also to ensure it is accessible at a price affordable for that country. As an example, daratumumab is available in India but the price is prohibitively high, allowing only the richest patients to use it. Greater use of registries and real-world evidence can help, and is indeed preferable, in situations where a clinical trial is clearly unethical or unfeasible to run. If new data emerge early during the course of a trial that proves the control group to be inferior, the system should be nimbler to allow quicker changes to protocols so that the control group continues to receive contemporary care. The recent Cape Town Statement arising from the World Conference of Research Integrity is a step forward in recognising unfair practices and inequity in research, as well as proposing principles and actions to foster equity in research moving forward. Nevertheless, many

For more on the **World Conference of Research Integrity** see https://wcri2022.org/

more steps and advocacy from the global community are needed. Until those steps are taken, we should recognise patients in control groups of clinical trials as another uniquely vulnerable population that requires our advocacy and attention.

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