Randomized controlled trials must be simplified to sustain innovation

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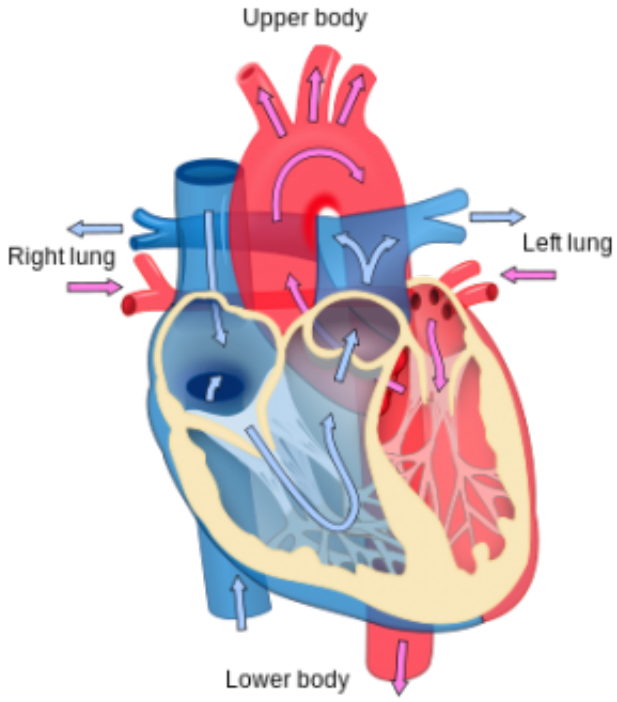

Heart diagram. Credit: Wikipedia

Randomised controlled trials must be simplified to sustain innovation in cardiovascular diseases, which are still the biggest killer in Europe, according to the Cardiovascular Round Table (CRT).

The CRT is an independent forum established by the European Society of Cardiology (ESC) and comprised of cardiologists and representatives

of the pharmaceutical, device and equipment industries. The group's views are published today in *European Heart Journal*.

Professor Paulus Kirchhof, corresponding author, said: "Despite marked progress in diagnosis and treatment, cardiovascular diseases are still the biggest killer in Europe and cause substantial morbidity and burden to the health care system. However, drug developers are opting to not develop new cardiovascular medicines, in part due to high perceived risk and development cost."

The paper published today outlines barriers to investing in cardiovascular research. The authors recommend new ways to conduct clinical research to make investment more attractive and bring drugs to market sooner.

The authors point out that the randomised controlled trial has transformed the practice of medicine and particularly of cardiovascular medicine. However, it has become bloated and inefficient and may be hindering cardiovascular drug development. Several specifics of cardiovascular medicine make investment into cardiovascular drugs less attractive than other fields of medicine, including:

- Many cardiovascular therapies require long term treatment to see any effect
- Demonstrating incremental risk reduction often requires very large sample sizes
- Cardiovascular disease encompasses a diverse range of mechanisms, not all of which are influenced by the agent studied making it difficult to identify patients likely to benefit
- Clinical trials are complex and subject to at times contradicting national and regional regulations

Professor Kirchhof said: "Cardiovascular drug development is partially a victim of its own success, where mortality benefits are the accepted

benchmark in the field, and new therapies have traditionally been evaluated in large cohorts. We have developed ever more robust systems to conduct such trials, and are now faced with a total cost that seems prohibitive for some of the novel developments. Progress in prevention of cardiovascular diseases may require more stratified or personalised management approaches in the future."

It costs up to $12 billion to bring a single drug to market and delays such as long regulatory reviews leave a short window to recoup costs before a patent expires. The authors state: "The impact of exclusivity loss should not be underestimated; it is increasingly considered a high-risk investment to fund outcome trials in cardiovascular medicine."

Other obstacles include the high cost when drugs fail in late stage clinical trials. The authors propose solutions to reinvigorate industry investment in cardiovascular research including targeted drug development and evaluation in defined patient populations, and simplifying large randomised trials.

Professor Kirchhof said: "We propose a streamlined pre-approval evaluation process for new cardiovascular medicines. We envision that a novel agent may initially be tested and approved for a smaller target population, underpinning the emerging concept of personalised cardiovascular medicine, and that further safety and efficacy data can be collected after the initial (conditional) approval. This will mitigate the risk for drug developers, and provide earlier access to novel therapies for patients."

He added: "Another, parallel approach would be to reduce the resource use in controlled trials, and to make use of modern IT based health and social records to collect information on death and severe cardiovascular outcomes, for example."

Professor Kirchhof concluded: "Novel approaches are urgently needed for developing new cardiovascular therapies to reduce the unacceptably high burden of disease. Regulators have an important role in making sure that only safe therapies are used in patients. This paper was developed with active involvement of the European Medicines Agency (EMA), which has recognised the problem we are trying to address. The ESC is confident that the EMA will be open to testing some of the novel solutions we propose."

More information: Improving clinical trials for cardiovascular diseases: a position paper from the Cardiovascular Round Table of the European Society of Cardiology. European Heart Journal. 2015; DOI: 10.1093/eurheartj/ehv2013 2Championing cardiovascular health innovation in Europe. *European Heart Journal*. 2013;34(33):2630-2635. DOI: 10.1093/eurheartj/eht211

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