

ORIGINAL ARTICLE

Modern clinical research: How rapid learning health care and cohort multiple randomised clinical trials complement traditional evidence based medicine

PHILIPPE LAMBIN, JAAP ZINDLER, BEN VANNESTE, LIEN VAN DE VOORDE, MARIA JACOBS, DANIELLE EEKERS, JURGEN PEERLINGS, BART REYEMEN, RUBEN T. H. M. LARUE, TIMO M. DEIST, EVELYN E. C. DE JONG, ANIEK J. G. EVEN, ADRIANA J. BERLANGA, ERIK ROELOFS, QING CHENG, SARA CARVALHO, RALPH T. H. LEIJENAAR, CATHARINA M. L. ZEGERS, EVERT VAN LIMBERGEN, MAAIKE BERBEE, WOUTER VAN ELMPT, CARY OBERIJE, RUUD HOUBEN, ANDRE DEKKER, LIESBETH BOERSMA, FRANK VERHAEGEN, GEERT BOSMANS, FRANK HOEBERS, KIM SMITS & SEAN WALSH

Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands

ABSTRACT

Background. Trials are vital in informing routine clinical care; however, current designs have major deficiencies. An overview of the various challenges that face modern clinical research and the methods that can be exploited to solve these challenges, in the context of personalised cancer treatment in the 21st century is provided.

Aim. The purpose of this manuscript, without intending to be comprehensive, is to spark thought whilst presenting and discussing two important and complementary alternatives to traditional evidence-based medicine, specifically rapid learning health care and cohort multiple randomised controlled trial design. Rapid learning health care is an approach that proposes to extract and apply knowledge from routine clinical care data rather than exclusively depending on clinical trial evidence, (please watch the animation: <http://youtu.be/ZDJFOxpWqEA>). The cohort multiple randomised controlled trial design is a pragmatic method which has been proposed to help overcome the weaknesses of conventional randomised trials, taking advantage of the standardised follow-up approaches more and more used in routine patient care. This approach is particularly useful when the new intervention is a priori attractive for the patient (i.e. proton therapy, patient decision aids or expensive medications), when the outcomes are easily collected, and when there is no need of a placebo arm.

Discussion. Truly personalised cancer treatment is the goal in modern radiotherapy. However, personalised cancer treatment is also an immense challenge. The vast variety of both cancer patients and treatment options makes it extremely difficult to determine which decisions are optimal for the individual patient. Nevertheless, rapid learning health care and cohort multiple randomised controlled trial design are two approaches (among others) that can help meet this challenge.

Tailored cancer therapies, in which specific information about patients and tumours is taken into account during treatment decisions, are an important step forward from current population-based therapy [1]. However, given the developments outlined below, it is becoming increasingly difficult to identify the best treatment for an individual cancer patient:

- 1) *Tumours and patients seem to be even less homogeneous than previously assumed*, meaning the same treatments can have different outcomes in patients who have the same type of tumour. For instance, there are at least four molecular subtypes of breast cancer, each with very different outcomes [2]. Based on gene signatures

various subgroups of tumours can be identified [3–8].

- 2) *The number of treatment options is increasing.* For example, early stage prostate cancer can now be treated with active surveillance, prostatectomy, external radiotherapy, stereotactic radiotherapy, low-dose rate (LDR) or high-dose rate (HDR) brachytherapy, high-intensity focused ultrasound, hormone therapy, combination therapies and so on. A different example is the recent rise of targeted therapies that are rapidly growing in numbers. Performing classic randomised trials to compare all new treatment options with the ‘gold standard’ is becoming impossible by the current speed of innovation.
- 3) *The evidence for the right choice in an individual patient is inadequate.* First, ‘evidence-based medicine’ and the ensuing guidelines always lag somewhat behind practice, particularly in highly technological, innovative and rapidly evolving fields, such as radiotherapy. In addition, translating the results of clinical trials to the general patient population and environment is not straightforward, given the higher quality of care in clinical trials and the known selection bias. Typically trials reach no more than 3% of cancer patients, in radiotherapy this is even lower [9–11] (An exception to this is the UK [12]). Finally, given the developments mentioned above – more treatment

options and less homogeneous patient groups – the urgency to scaffold our treatment decisions with robust knowledge and the demand for evidence-based medicine is larger than ever.

- 4) *It is becoming more difficult to find the right evidence.* Despite – or perhaps due to – the fact that papers are being published in rapidly increasing numbers (e.g. a radiation-oncologist specialising in lung cancer must read roughly eight articles per day to keep up with the literature [13]), it is difficult to match the characteristics of the individual patient to evidence from the literature and to evaluate the quality of that evidence.

The developments illustrated above have given rise to a search for alternatives to the elaborate consensus- and evidence-based guideline medicine format when it comes to making treatment decisions.

Aims

The aim of this paper, without intending to be comprehensive, is to present and discuss two leading and synergistic alternatives to the status quo, namely rapid learning health care (RLHC) [14] and cohort multiple randomised controlled trial (cmRCT) design [15]. RLHC is known under various names, including knowledge-driven medicine, computer-assisted theragnostics and intelligent medical

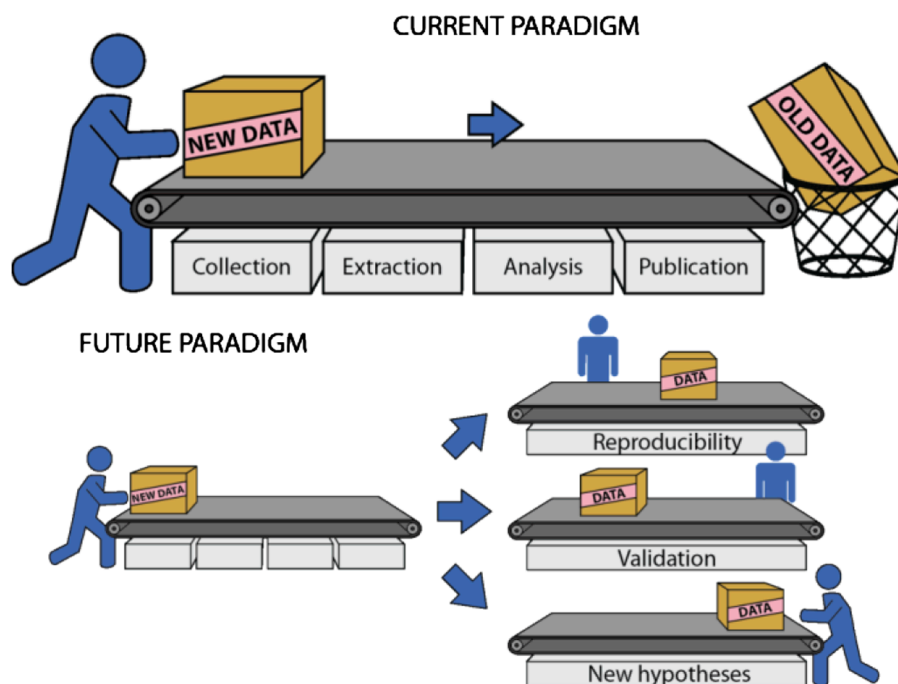


Figure 1. Current paradigm versus future paradigm, modified from [25].

networks, however, the basic idea in all cases is the (re)use of historical data from routine clinical practice for decisions concerning new patients or to test new hypothesis [16–20] (Figure 1).

cmRCT design is a large observational cohort of patients recruited and used as a multiple trials facility; each randomised controlled trial uses random allocation of some participants (not random allocation of all); and patient-centred information and consent is applied (Figures 4 and 5). This paper is intended to encourage innovation and provides an overview of these two approaches.

Other promising approaches, such as innovative bio-statistical techniques were deemed beyond the scope of this work [21–23].

Rapid learning

RLHC is accomplished in four iterative and infinitely repeated stages [14] (Figure 2). The *Data* stage is concerned with the acquisition and extraction of previous patient data, including their delivered treatments and outcomes. The *Knowledge* stage employs advanced analytical techniques, such as machine learning, to generate knowledge from the collected data. The *Application* stage utilises this knowledge to enhance clinical practice. The *Evaluation* stage assesses outcomes, after which the first stage begins again. In each stage, external knowledge (e.g. from clinical trials) is used to optimise the stage. The sections below describe each stage in detail.

Data

Idealised RLHC necessitates the ‘4 V’s’ of ‘Big Data’; volume, variety, velocity, and veracity of data. The volume of data is important: 1) to acquire superior knowledge (the quality of the knowledge correlates with the number of patients on whom that knowledge is based); and 2) to discern knowledge regarding fewer, more homogeneous patient groups and/or use more variables in the knowledge stage. The variety of data (principally in relation to treatments used, but also in terms of patient characteristics) is key to ultimately determine which treatment is optimal for an individual patient. The velocity of data is important to ensure that knowledge is garnered as dynamically and as continuously as possible, while the veracity of data is essential to the level of confidence that can be attributed to the knowledge obtained. Obtaining data of sufficient quality with respect to the ‘4 V’s’ is the greatest challenge in RLHC. Academic and community healthcare systems must adopt a data sharing philosophy [24], across institutional and national borders, in order to meet this challenge [25]. Obstacles to data sharing comes in the guise of: human resources or a lack of time; linguistic and cultural differences as well as data recording practices; the academic and political value of data; risks to reputation; privacy and legal aspects and so on. Nevertheless, a joint venture connecting radiotherapy institutes in the Netherlands, Germany and Belgium successfully implemented RLHC through data sharing in the euroCAT project (www.eurocat-project.eu).

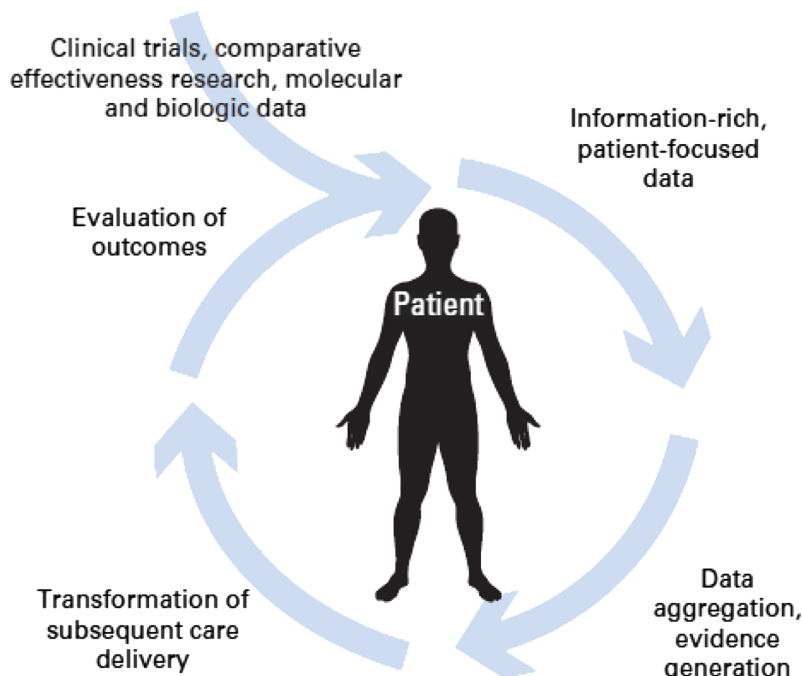


Figure 2. The four stages of RLHC, modified from [14].

eurocat.info, please watch the animation). Advanced and innovative information technologies were fundamental to the success of the project, enabling simultaneous RLHC in each centre without the data having to leave the institution (a concept known as *distributed learning*). This required the creation of data with semantic interoperability (also known as ‘data with linguistic unity’ or ‘machine-readable data’), in which local terms are mapped to concepts from a well defined ontology (e.g. NCI Thesaurus). With this method, the ontology terms act as a communal interface to the data at each institutional site, allowing a collective method for information retrieval and reasoning enabled through a semantic portal to the data. A benefit of such enterprises is that they promote increasing coordination with respect to what data needs to be collected and how (i.e. disease-specific ‘umbrella’ protocols) [26].

Knowledge

Machine learning generates knowledge from data. In machine learning, models/algorithms are utilised to best describe existing data and produce knowledge which can be leveraged to make predictions with respect to new, unseen data. Models trained on historical data may be used to predict the outcomes (e.g. survival, quality of life, toxicity, etc.) of various treatments on the basis of data from a new patient. An un-validated model is of very limited value and it is therefore necessary that models are adequately validated [27–31]; Hence, a validation dataset should always be available, preferably from an institute different (but not unsuitably dissimilar) than that from which the data was used to create the model.

Examples of radiotherapy models (on the basis of both clinical trials and RLHC) are available for non-small cell lung, rectal and head-and-neck cancer on <http://www.predictcancer.org>, breast cancer on <http://research.nki.nl/ibr/>, prostate cancer on <https://www.mskcc.org/nomograms/prostate>, and glioblastoma on <http://www.eortc.be/tools/gbmcalculator/>.

Application

The knowledge produced by RLHC is applied with the assistance of Decision Support Systems (DSS). These are typically software applications that can be employed to apply knowledge-driven healthcare in practice. Examples include nomograms [32,33] and websites, such as those named above (Figure 3).

DSS are intended to aid the physician and the patient in making the most informed decision possible with respect to treatment choices (They are neither intended nor suited as a replacement to the physician in the wider healthcare context). Healthcare professionals exploiting computer models is, of course, not new in radiation oncology. Physics-based models for dose computation as well as radiobiology-based normal tissue complication probability (NTCP) [34] and tumour control probability (TCP) [35] models to relate dose with toxicity and tumour control, are all well established within the radiotherapy community. The emergent models from RLHC [36] are a natural extension. A key aspect of RLHC models is their ‘holistic’ and multifactorial nature, incorporating the current physics- and/or radiobiology-based models, as well as taking into account patient, tumour and non-radiotherapy

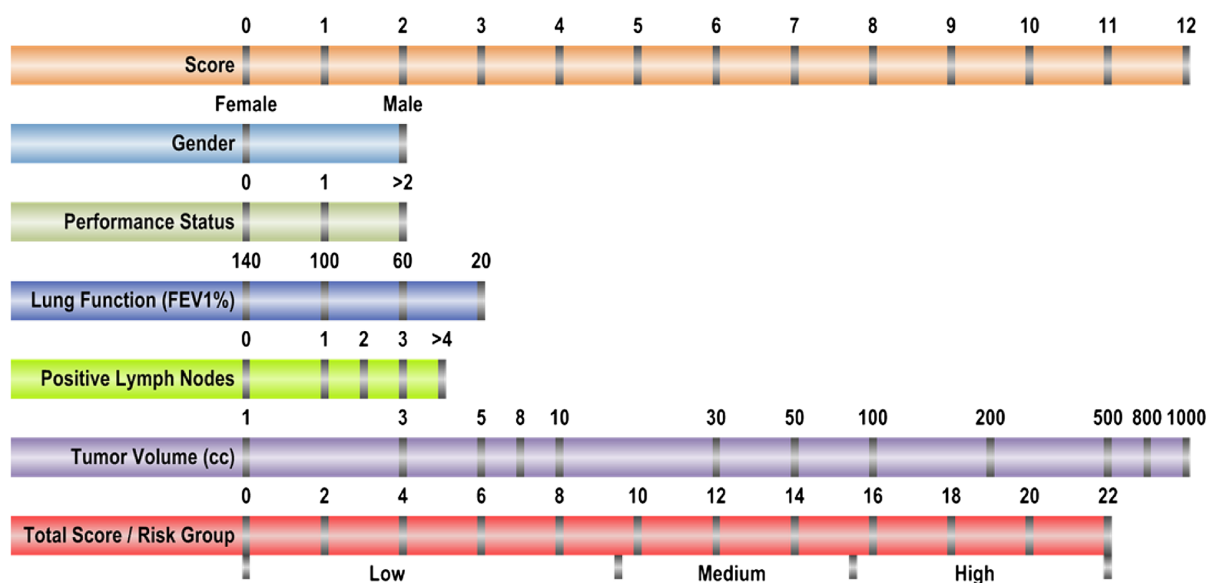


Figure 3. Example of a nomogram for two-year survival of non-small cell lung cancer patients treated with chemoradiotherapy, modified from [16].

factors [37]. For example, a RLHC model of radiation-induced esophagitis estimates that the risk for this toxicity not only depends on the dose to which the oesophagus is exposed, but also greatly increases if chemotherapy is administered concomitantly [38]. Another instance is that for non-metastatic irresectable non-small cell lung carcinoma, the prognostic value with respect to survival is better predicted by a multifactorial model based on clinical, imaging and biomarkers variables than TNM classification [39]. Though, the addition of prognostic factors does not always result in better outcome prediction, so critical comparison of complex multifactorial models with relatively simple commonly used models is essential to determine the exact value of additional prognostic factors [40]. Moreover, it is important to stratify models for treatments which are conceptually completely different, such as whole brain radiotherapy and radiosurgery in brain metastases patients, in which TCP and NTCP differ substantially [41–43].

Evaluation

The core idea in RLHC is that the application of knowledge attained from routine data leads to profound understanding and consequently a predictability of treatment outcomes, implying that these outcomes can be enhanced both in terms of effectiveness (achieving the desired result) and efficiency (the resources needed to achieve the result). Certainly, RLHC models must be continuously evaluated (as with all models confounders and selection bias are issues), concentrating on the questions ‘Is the outcome of the treatment as predicted, and if so, how does this compare with consensus- and evidence-based guideline knowledge?’. This evaluation should preferably be conducted with (meta-analysis of) robust data that is independently interpreted by multiple stakeholders (including healthcare economists and patient representatives).

Cohort multiple randomised controlled trial

Several alternative trial designs have attempted to address the issues of RCT recruitment, ethics and patient preferences, as well as treatment comparisons, such as the patient preference [44], comprehensive cohort [45,46] and randomised consent (Zelen) designs [47]. However, these designs also have limitations. Within the trial design community the question of which trial design best overcomes these challenges is currently not settled, comparative data is required to definitively answer this, and it may be the case that in the future specific trial designs are selected from an arsenal of trial designs tailored to specific questions. However, after review of the lit-

erature and discussion with experts *it is our opinion* that the cmRCT design was the most attractive single option to solve the main challenges of evidence for personalised medicine. cmRCT design has three key features intended to overcome some of the limitations of existing trial designs. The sections below describe the cmRCT and address the previously stated limitations in detail.

The key features of cmRCT design are:

- 1) Recruitment of a large observational cohort with a specific ailment.
- 2) Patient-centered informed consent relevant to routine clinical care.
- 3) Multiple randomised controlled trials over time with systematic measurement of outcomes for the complete cohort.

The cmRCT design can be briefly summarised as follows. A large observational cohort of patients with a specific ailment is recruited (N0). Next, for each initiated randomised controlled trial, information from the cohort is used to ascertain all eligible patients (N1). Some eligible patients (n1) are randomly assigned and offered the trial intervention. The outcomes of these randomly assigned patients (n1) are then evaluated with the outcomes of eligible patients not randomly assigned, i.e. those receiving standard care (N1–n1). This method can be repeated ad infinitum resulting in a single cohort with multiple randomised controlled trials (e.g. 1, 2, 3, 4, etc.). Figure 4 displays the cmRCT design while Figure 5 illustrates an example cmRCT in practice.

Recruitment

With respect to recruitment, many randomised controlled trials struggle or fail to recruit adequate patient numbers resulting in potentially under-powered and non-generalisable trial findings. Additionally, numerous clinical trials omit minority groups [48], leading to differences in the clinical care population and the trial population [49]. Estimates of efficacy in routine clinical scenarios are necessary. If the clinical care population is under-represented in a trial which reports variable efficacy, then subsequent analyses cannot truthfully inform future decisions in the clinical care population. In the cmRCT design, however, the problem of recruitment is met by automatically including all patients into the cohort, key feature I. Inclusion requires that each patient consents at the outset to provide data to be used to look at the benefit of treatments for the condition of interest.

Ethics and patient preferences

Ethical issues relating to concerns with information and consent [50] are cited by patients (and clini-

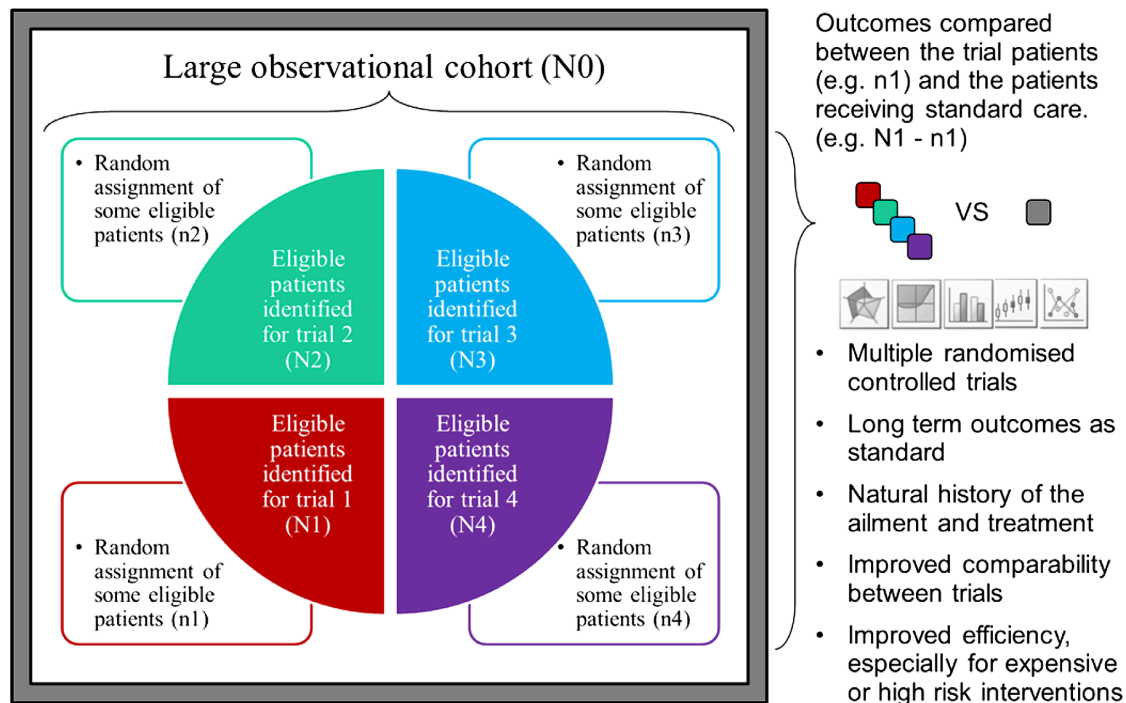


Figure 4. Example of the cmRCT design, modified from [15].

cians) as the primary reason for non-participation in clinical trials. Researchers and clinicians should comply with local habits and ethical rules. However, in routine clinical care, patients are sub-optimally informed of treatment options that their clinicians cannot with certainty provide [51,52], nor are patients informed that their treatment will be decided

by chance. Conversely, in clinical trials it is viewed as an ethical requirement to provide this information prior to randomisation. The rationale of randomisation in clinical trials is to create groups where assignment and treatment can be purely attributed to chance, with all known/unknown baseline prognostic factors equally distributed. Randomisation is gener-

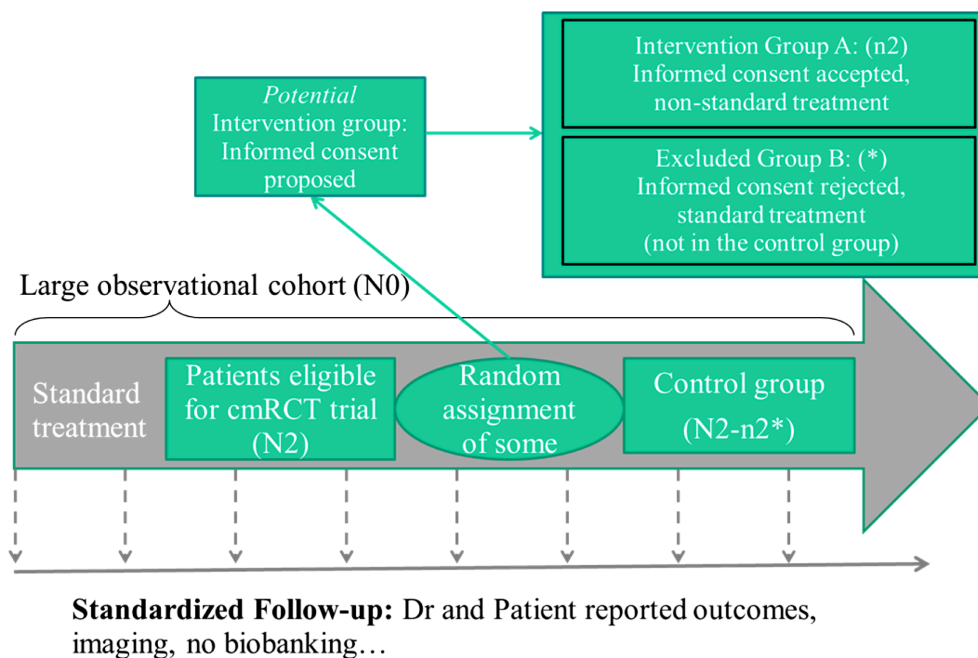


Figure 5. Flowchart of an example cmRCT in practice, modified from [53].

ally conceived as a random allocation of all patients and accordingly necessitates prior consent. However, generating groups where assignment is a consequence of pure chance can be achieved by random assignment of some patients and therefore prior consent of only some patients and not all patients is necessary.

These issues are met in the cmRCT design by key feature II. The implementation of patient-centered informed consent, where the method of providing information and attaining patient consent strives to duplicate routine clinical care rather than adhere to the requirements of trial design. All patients within the large observational cohort consent to provide observational data at the outset; however, consent for a particular possible intervention is required only from patients offered that intervention, thus replicating the patient-centered information and consent procedures that occur in routine clinical care, where clinicians provide patients with appropriate information at the appropriate time.

There are two justifications for this approach. Firstly, the principal motivation of patients participating in clinical trials is their own direct benefit and therefore informed consent procedures should place the needs of the patient at the fore, i.e. patients should not be told about treatments that they might not then receive, nor should they be told that their treatment will be assigned by random chance. Second, the smaller the disparity between patients' experiences in trials and their experiences in routine clinical care, the greater the generalisability of the trial results to patients in routine clinical care.

Treatment comparisons

An archetypal research problem is that of determining which potential treatment is optimal. Historically, each potential treatment has been trialed, independently, in diverse populations by different institutions. This method has resulted in numerous trials of different interventions, with dissimilar trial populations and frequently short term and varied outcomes—a method that is becoming evidently unsustainable as the number of treatment options increases.

Key feature III, multiple randomised controlled trials over time with systematic measurement of outcomes for the complete cohort, has two desirable characteristics with respect to the concerns highlighted above. Firstly, an abundance of long-term follow-up improves the detection of uncommon adverse late effects which develop long after treatment. Second, enriched homogeneity within the cmRCT populations is ensured therefore augmenting the generalisability of the results as well as facilitating direct comparisons.

It is clear that the cmRCT design is not suited for all types of trials or questions: it is particularly suitable

when the experimental treatment is expensive or attractive (e.g. proton therapy), the comparator is the standard treatment and no translational research is required. It is not suited to double blind randomised trials, when translational research is compulsory or when the outcome is hard to collect (Table I). To the best of our knowledge, there is only one example of a cmRCT trial tackling a radiotherapy question, the RECTAL BOOST study conducted in Utrecht, the Netherlands [53]. The trial investigates pathological complete response rate, clinical response, toxicity, quality of life and (disease-free) survival in locally advanced rectal cancer patients treated with 65Gy (boost + chemoradiation) compared with 50 Gy standard chemoradiation. The cmRCT design provides the opportunity to overcome common shortcomings of classic randomised controlled trials, such as slow recruitment, disappointment-bias in control arm patients and poor generalisability.

Discussion

Personalised cancer treatment is a necessity, to guarantee not only that patients receive the treat-

Table I. Requirements and conditions for a cmRCT.

Most suited to:	Least suited to:
Design	
• Open trials with 'standard treatment' as the comparator • Studies that aim to inform healthcare decisions in routine practice (pragmatic trials) • Research questions that address easily measured and collected outcomes • Translational research not needed	• Closed trial designs with placebo arm • Studies that aim to further knowledge as to how and why a treatment works (efficacy trials) • Research questions that address hard to measure and hard to collect outcomes (e.g. repeated biopsies, unusual imaging) • Translational research needed
Inclusion criteria	
• Stable populations • Easily identified populations	• Populations with high attrition • Unstable patient populations (the standard protocol changes regularly) • Difficult to identify populations
Type treatment	
• Treatments highly desired by patients (e.g. proton therapy, new drug, patient decision aids...) • Expensive treatments (e.g. proton therapy, immunotherapy...)	• Treatments not highly desired by patients (e.g. toxic, mutilating treatment)

ment that best suits his or her healthcare status (as well as avoiding under or overtreatment) but also that the right resources are being diverted to the right patients [54]. However, personalised cancer treatment is also a challenge: the enormous variety in cancer patients and treatments implies that it is by no means always clear which choices lead to which treatment outcomes. Particularly in scenarios where numerous treatments choices are possible with no clear cut clinical advantage in outcome, a shared decision making process can be employed in order to make the most of patient preferences.

This also holds for radiotherapy. The radiosensitivity of tumours and normal tissues is typically unknown, due to both intra- and inter-patient heterogeneity [55,56]. Furthermore, the range of treatment choices and thus decisions that must be made within radiotherapy have sharply risen, principally due to technological innovations, such as IMRT, VMAT, IGRT, and particle therapy. Opting for a particular radiation technology, techniques, dose/fractionation, as well as innovative combinations

with systemic and targeted treatments such as Tyrosine-Kinase inhibitors (e.g. sunitinib) or monoclonal antibodies (e.g. cetuximab), on the basis of expected outcomes is therefore difficult, and the established guidelines and literature provide only limited support in this regard.

This article presents and discusses two specific approaches which can augment traditional evidence-based medicine to meet and overcome these challenges. RLHC and cmRCT can provide support when determining personalised cancer treatment. In essence, RLHC involves (re)using routine clinical care data to acquire knowledge in the form of models that can predict treatment outcomes, and then clinically applying and carefully evaluating these models by way of DSS. The hypothesis is that treatment outcomes obtained in the past can be used to predict future results.

The RLHC method seems to contradict the principles of evidence-based medicine, in which treatment decisions are based solely on results obtained from controlled clinical trials. In fact it does not; both approaches are complementary (Fig-

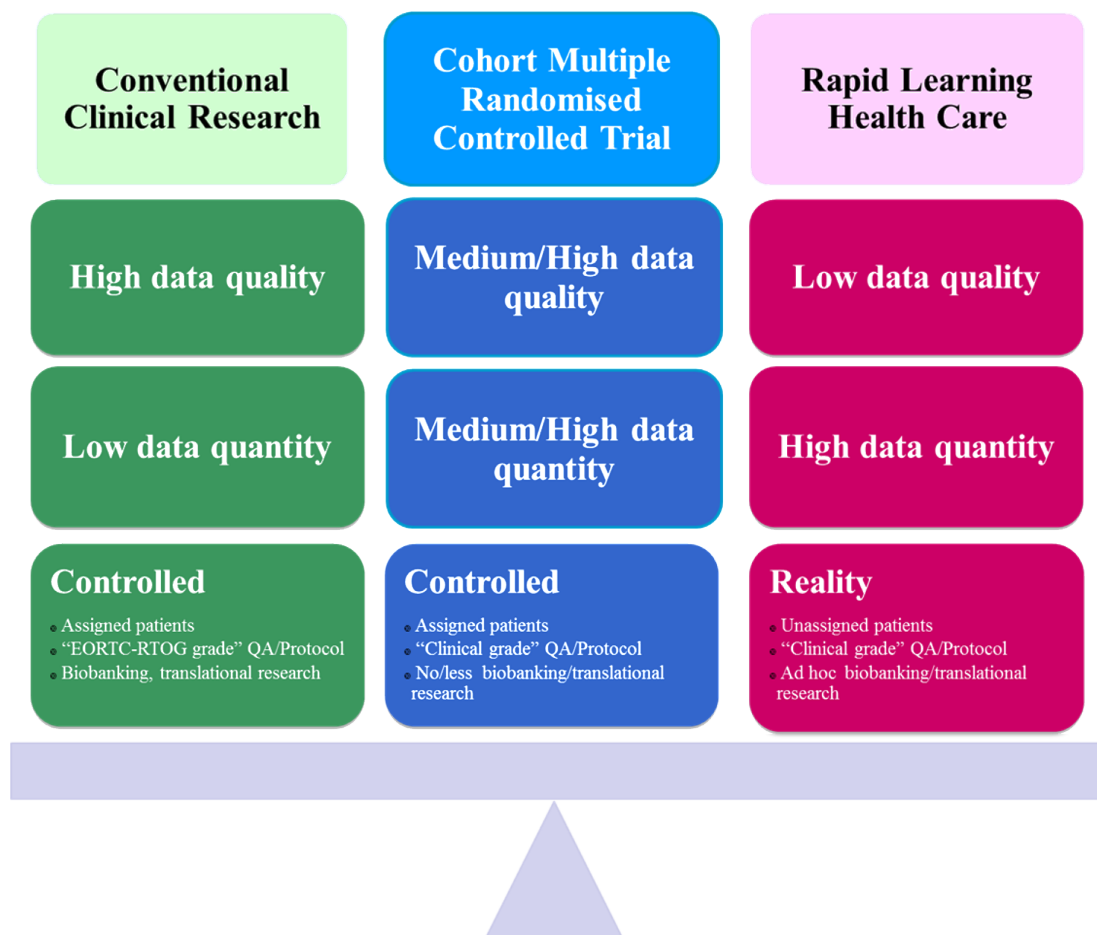


Figure 6. Complementary instead of contradictory approaches: cmRCT can be seen as an intermediate approach between conventional clinical trials and RLHC.

ure 6). This is compounded by the fact that RLHC is based on results obtained from the less controlled setting of routine clinical care. These different environments yield different insights. Controlled clinical trials primarily aim to identify small improvements in results between two treatments in a patient group that is as homogeneous as possible. In contrast, RLHC will reveal major differences in treatment outcomes that stem from the heterogeneity of the patient group. It will be inferior in detecting minor differences in treatments due to the lower quality of the data in clinical practice as compared to the same treatment in a clinical trial. In addition, RLHC can be seen as an alternative for situations in which there is insufficient evidence to make decisions in line with the principles of evidence-based medicine. This is often the case with technological innovations, i.e. when considering the use of new techniques (e.g. IMRT, protons) in the field of radiotherapy.

RLHC is a new development that still needs to prove its value as a supplement to traditional evidence-based approaches. Radiotherapy seems to be the ideal setting to study the value of RLHC, given the field's high degree of computerisation as well as its long use and acceptance of predictive models. Within clinical radiotherapy, models and planning systems should become available that make it possible to not only plan on the basis of physical dose and dose-volume histogram parameters, but also to explain the relationship with the expected clinical outcomes in individual patients. Translating knowledge to an individual patient is challenging, particularly in so-called preference-sensitive situations where trade-offs between options with more or less equally desirable outcomes, but which different individuals may value differently, e.g. in terms of side effects. Due to better access to health-related information patients have an increased desire to be in charge of their own life and health. Despite investment in efforts to improve the skills of clinicians, patients continue to report low levels of involvement [57]. There is indeed evidence level 1 from a Cochrane systematic review evaluating 86 studies involving 20 209 participants included in published randomised controlled trials demonstrating that decision aids increase people's involvement, support informed values-based choices in patient-practitioner communication, and improve knowledge and realistic perception of outcomes. We therefore believe the next step will be to integrate, whenever possible, shared decision making approaches (see, e.g. www.treatmentchoice.info; www.optiongrid.org) to include the patient perspective on the best treatment of choice [33].

The cmRCT design is also a new development that still needs to prove its value as a supplement to traditional evidence-based approaches, however, the cmRCT design does help solve some of the flaws of current trial design by delivering robust evidence that clinicians can utilise in routine clinical care populations [15,58]. Harmonised with randomised controlled trials, longitudinal observational studies can recruit superior numbers and a more representative sample of patients. Additionally, the cmRCT design enables more applicable direct and indirect comparisons than is possible with trials conducted using conventional randomised controlled trial designs due to all treatments having the same 'standard treatment' comparator and key outcomes. Furthermore, the large observational cohort recruited in the cmRCT design escalates statistical power and enables unequal randomisation. For example, a few patients could be randomly assigned and offered an expensive treatment (e.g. proton therapy, immunotherapy) and compared with a greater number of unassigned patients. Unequal randomisation thus improves the effectiveness of trials of high cost interventions compared with equal allocation. These features reinforce the inferences in the trial, reduce treatment costs compared with standard designs (i.e. when the cohort is setup, it permits swift and economical recruitment of patients for any randomised controlled trials), and allows substantial cost savings in trials of expensive treatments. Finally, data with respect to treatment refusers affords useful information with regard to the acceptability of the treatment and accordingly the generalisability of the trial results.

However, it is therefore not only new trial designs that are required but also new strategies and methods to apply new knowledge in the clinic, these new approaches should be both hypothesis and outcome-data driven with appropriate evaluation and assessment. There can be significant time gaps between changes in scientific knowledge and changes in clinical guidelines and practice. A pressing issue in radiation oncology is that the most clinically relevant endpoints are commonly five or even 10 year results. During this period treatment strategies advance and evolve introducing a confounding factor 'with the current treatment, the result of the trial would be different!' Therefore there is a pressing need for earlier surrogate endpoints, RLHC can help find and test these surrogate endpoints.

RLHC and cmRCT are synergistic approaches (among others not explored here) and can complement traditional evidence-based medicine with regard to progressing both scientific knowledge and clinical practise.

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