Research article

Linking CHHiP prostate cancer RCT with GP records: A study proposal to investigate the effect of co-morbidities and medications on long-term symptoms and radiotherapy-related toxicity

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Article info

Article history:
Received 21 March 2017
Received in revised form 17 May 2017
Accepted 7 June 2017
Available online 27 June 2017

Keywords:
Data linkage
Radiotherapy-related side-effects
Late-effects
CHHiP
RCGP RSC
Big data

ABSTRACT

Background: Patients receiving cancer treatment often have one or more co-morbid conditions that are treated pharmacologically. Co-morbidities are recorded in clinical trials usually only at baseline. However, co-morbidities evolve and new ones emerge during cancer treatment. The interaction between multi-morbidity and cancer recovery is significant but poorly understood.

Purpose: To investigate the effect of co-morbidities (e.g., cardiovascular and diabetes) and medications (e.g., statins, antihypertensives, metformin) on radiotherapy-related toxicity and long-term symptoms in order to identify potential risk factors. The possible protective effect of medications such as statins or antihypertensives in reducing radiotherapy-related toxicity will also be explored.

Methods: Two datasets will be linked. (1) CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer) randomised control trial. CHHiP contains pelvic symptoms and radiation-related toxicity reported by patients and clinicians. (2) GP (General Practice) data from RCGP RSC (Royal College of General Practitioners Research and Surveillance Centre). The GP records of CHHiP patients will be extracted, including cardiovascular co-morbidities, diabetes and prescription medications. Statistical analysis of the combined dataset will be performed in order to investigate the effect.

Conclusions: Linking two sources of healthcare data is an exciting area of big healthcare data research. With limited data in clinical trials (not all clinical trials collect information on co-morbidities or medications) and limited lengths of follow-up, linking different sources of information is increasingly needed to investigate long-term outcomes. With increasing pressures to collect detailed information in clinical trials (e.g., co-morbidities, medications), linkage to routinely collected data offers the potential to support efficient conduct of clinical trials.

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Abbreviations: ANOVA, analysis of variance; BNF, British National Formulary; CHHiP, Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer; EPIC, Expanded Prostate Cancer Index Composite; FACT-P, Functional Assessment of Cancer Therapy-Prostate; GP, General Practitioner; GEE, Generalized Estimating Equations; ICD10, International Classification of Disease version 10; ICR, Institute of Cancer Research; IMRT, Intensity Modulated Radiotherapy; LENT/SOMA, Late Effects Normal Tissue Toxicity; subjective, objective, management, and analytic; PCa, Prostate cancer; PROs, Patient Reported Outcomes; QOL, Quality of life; RCGP, Royal College of General Practitioners; RCT, Randomised Control Trial; REC, Research Ethics Committee; RSC, Research & Surveillance Centre; RTOG, Radiation Therapy Oncology Group; SHA2-512, Secure Hash Algorithm 2 with 512 bit hash values; UCLA-PCI, University of California, Los Angeles Prostate Cancer Index; UK, United Kingdom.

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http://dx.doi.org/10.1016/j.tipsro.2017.06.001
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Introduction

High doses of radiation are needed to cure most common cancers. Radiotherapy is planned with a "safety margin" to account for any tumour or patient movement during treatment. This inevitably leads to the inclusion of some healthy normal tissue in the treatment target area which can lead to radiation damage and side-effects [1]. Modern radiotherapy techniques can conform radiation dose more precisely to fit the shape of the cancer. In addition, these image-guidance methods make treatments more accurate. These methods improve tumour targeting so they have significantly reduced toxicity [2,3]. However, serious adverse-effects and reduced quality of life (QOL) are still observed in a small number of patients [4–7]. Dose escalation to improve cancer cure can also increase morbidity. Radiation side-effects and symptoms often emerge many months or years after treatment (late-effects) and may be difficult to investigate or manage.

Late-effects are a key concern to oncologists, as 84% of prostate cancer (PCa) patients survive at least ten years [8] and avoidance of long-term side-effects remains a clinical challenge. As the survival rate is relatively high, PCa is now commonly described as a chronic and slowly progressing disease. It is therefore crucial to understand the long-term healthcare needs of this ageing population of patients and the impact of co-morbidities in the management of side-effects [9]. PCa is the most frequently diagnosed male cancer in the United Kingdom (UK) with almost 50,000 new cases each year [8]. External beam pelvic radiotherapy (EBRT) alongside surgery is the main form of treatment and it is often used in conjunction with hormone therapy [10].

The most common side-effects of pelvic radiotherapy are those experienced from gastrointestinal and genitourinary systems. The most troublesome of the range of early reported short-term side-effects are dysuria, haematuria, irritation and inflammation of the skin, bowel, bladder or rectum. These side-effects are caused directly by irradiation, and they usually improve quickly after treatment [5,11]. Late side-effects occur from 6 months to several years after treatment. The most common long-term side-effects include urinary obstruction, incontinence, bowel frequency, proctitis and sexual problems [7,12–14]. These side-effects, similarly to the short-term ones, are also caused by damage from the radiation and the resulting vascular changes. However, they are usually long-term and therefore have a significant impact on the QOL. Inflammation is closely associated with increased acute toxicity, and is also linked to late toxicity (as consequential late-effects) [15]. The link of long-term side-effects with short-term is not fully defined but short-term side-effects have been identified as a precursor of long-term [16]. For this reason it is important to act as early as possible to prevent and reduce side-effects.

There are two areas of research that are of interest regarding co-morbidities and concomitant medications for cancer patients. One is that co-morbidities result in worse health-related outcomes for radiotherapy patients [2,3,17–20]. A recently completed systematic literature review on radiotherapy in diabetic patients identified diabetes as a negative factor and highlighted the need for more research [17]. Another stem of evidence leads to the effect of cardiovascular medications and improved late toxicity [21–25]. Statins have been found to improve health-related outcomes post-radiotherapy [26–33]. Evidence suggests that those medications may protect against normal tissue injury caused by radiation [27–31].

Materials and methods

Aims

The aim of this study is to investigate the effect of co-morbidities (focusing on cardiovascular diseases and diabetes) and prescription medications (cardiovascular medications such as statins, anticoagulants, heart medications, antihypertensives, erectile dysfunction as well as diabetes medications e.g. metformin) on symptoms and radiotherapy-related side-effects in PCa patients. Two sources of healthcare data will be pulled together to study long-term symptoms and toxicity in relation to co-morbidity. General Practice (GP) medical history will be extracted for CHHiP patients. CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer, CRUK/06/16) is a large PCa radiotherapy randomised controlled trial (RCT) [34,35]. Patients recruited to CHHiP were randomised to three different radiotherapy schedules and were monitored over time. Therefore, long-term patient reported outcomes (PROs) and clinician recorded radiotherapy-related symptoms and toxicity data are available. The focus will be on urinary, rectal and sexual symptoms and toxicity. The GP dataset that will be used is a dataset of the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) [36].

Using de-identified (irreversibly hashed) NHS numbers (already collected with consent in the CHHiP trial), GP records on co-morbidities and prescription medications before, during, and after radiotherapy will be retrieved for CHHiP patients. CHHiP prospectively collected longitudinal data on radiotherapy-related symptoms and toxicity (follow-up up to 5 years) reported both by patients (PROs) and clinicians. Table 1 details the type of data extracted and linked from GP records and CHHiP trial. The resulting linked dataset will be used to investigate the effect of co-morbidities and concomitant medications on symptoms and radiotherapy-related side-effects.

Dataset

CHHiP clinical trial

CHHiP (CRUK/06/16, REC reference 04/MRE02/10) trial [34,35] is conducted by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU). It is a dataset of 3216 men with PCa recruited from 71 centres in the UK, Republic of Ireland, Switzerland, and New Zealand between October 2002 and June 2011. Men were randomised to three different conformal Intensity Modulated Radiotherapy (IMRT) dose schedules: the standard schedule of 74 Gy (37 fractions(f)) given over 7.5 weeks, or two hypofractionated and shorter schedules, doses of 60 Gy (20f) or 57 Gy (19f). The trial tested the hypothesis that hypofractionated radiotherapy schedules for localised PCa would improve the therapeutic ratio by either improving tumour control or reducing normal tissue side-effects. It demonstrated non-inferiority of the 60 Gy/20f schedule (compared to 74 Gy/37f) in terms of biochemical/clinical failure with similar and low rates of toxicity [34,35].

Patients were followed-up over time, and short-term and long-term PROs and clinician-reported radiotherapy-related toxicity data are available. The median follow-up of patients is 62.4 months (IQR: 53.9–77.0). PROs were collected (as previously described elsewhere [37,38]) with the UCLA Prostate Cancer Index (UCLA-PCI) [39], Short Form (SF)-36 [40], and Functional Assessment of Cancer Therapy-Prostate (FACT-P) [41] questionnaires. In March 2009 UCLA-PCI, FACT-P and SF-36 were replaced by the Expanded Prostate Cancer Index Composite (EPIC) [42] and SF-12 [35]. Clinician reported toxicity data were collected with the Radiation Therapy Oncology Group (RTOG) [43], the Late Effects Normal Tissue Toxicity; subjective, objective, management, and analytic (LENT/SOMA) [44]. In this study, the focus is on symptoms and toxicity in the three health domains (urinary, bowel and sexual) that are most affected by PCa and its treatment.

Only the UK CHHiP population of patients (N = 3179) will be included in this study. The non-UK patients will be excluded because there are no NHS numbers for these patients. Patients
from recruitment centres in Wales, Scotland and Northern Ireland will be included, even though the RCGP RSC contains records from English GPs only. This is to create a nationally representative resource. The RCGP RSC is representative of the whole UK population [36]. To evaluate the representativeness of the linked subsample, the analysis will include comparisons of linked records to non-linked CHHiP patients and to the RCGP RSC population. Another reason to include all the UK CHHiP patients is that there are other GP databases (aside from RCGP RSC) that could be linked to CHHiP as a follow-on from this project. This offers the opportunity to follow-up patients from regions that are not available in RCGP RSC. In addition, GP data may be available in RCGP RSC for some of these patients if for example they had previously been registered with an English GP.

In order to support the linkage of CHHiP to other data sources, NHS numbers (CHI numbers in Scotland) were collected. Co-morbidities were recorded at baseline and included diabetes, hypertension, inflammatory bowel disease, previous pelvic surgery, symptomatic haemorrhoids and previous TURP (transurethral resection of the prostate). With regard to prescription medications, the information on cardiovascular conditions such as statins, anticoagulants, heart medications, antihypertensives, erectile dysfunction medications diabetes medications eg. metformin, antimuscarinics or alpha blockers, rectal steroids, Records of hospital procedures (if recorded): cystoscopy, TURP, bladder neck incision, salvage prostatectomy, hip fracture, hip replacement, sigmoidoscopy, colonoscopy, argon laser coagulation, hyperbaric oxygen, records of prescribed incontinence pads.

| Source of data | Type of data extracted | Timelines |
|---------------|------------------------|-----------|
| (A) RCGP RSC GP records | Records of co-morbidities: cardiovascular conditions, diabetes, Records of prescription medications: cardiovascular medications such as statins, anticoagulants, heart medications, antihypertensives, erectile dysfunction medications diabetes medications eg. metformin, antimuscarinics or alpha blockers, rectal steroids, Records of hospital procedures (if recorded): cystoscopy, TURP, bladder neck incision, salvage prostatectomy, hip fracture, hip replacement, sigmoidoscopy, colonoscopy, argon laser coagulation, hyperbaric oxygen, records of prescribed incontinence pads | Over time: from 3 months before the start of radiotherapy during radiotherapy after radiotherapy (all data that is available) |
| (B) CHHiP clinical trial | Patient and clinician-reported cancer and radiotherapy-related function, symptoms, bother, QOL and toxicity for the following health domains: urinary, rectal, erectile, general health, physical function (Detailed list of tools and specific domains is in Table 2) | Longitudinal, the following time points will be extracted: initial assessment - pre-hormone therapy (baseline) pre-radiotherapy 10 weeks after the start of radiotherapy (acute) every 6 months, up to 2 years after the start of radiotherapy (long-term) toxicity with RTOG collected weekly during radiotherapy and then at 10, 12, 18 weeks and 12 months after radiotherapy |

RCGP RSC

The RCGP RSC [36] has been collecting primary care data in England, and monitoring disease trends for almost 60 years. The network of practices currently includes 192 GP practices with a total number of about 1.5 million active patients (1.5% of the English population). Data are extracted weekly from GP practices in the network, covering the past 6 weeks of data. Every four months, a bulk extract is conducted where historical data for all registered patients are extracted. All patient personally identifiable data are pseudonymised (de-identified) as close as possible to the point of extraction from GP databases. The information that will be extracted from GP records for CHHiP patients will include co-morbidities (cardiovascular and diabetes) and medication history taken for these conditions before, during and after radiotherapy. Cardiovascular medications such as statins, anticoagulants, antihypertensives, heart medications, erectile dysfunction as well as diabetes medicines such as metformin will be included. Table 1 summarises the type and time points of data extracted from both sources. RCGP RSC has granted permission to conduct this project (Data request RSC_0315). An NHS ethics approval has been obtained from the West of Scotland REC1 (16/WS/0076).

Study design

The study will be undertaken in the following four stages.

De-identification (pseudonymisation) of CHHiP data

All patient personally identifiable data will be de-identified before the transmission of CHHiP data to the University of Surrey. NHS numbers will be hashed, dates of birth will be hashed, and postcodes converted into Lower Super Output Areas (LSOAs) at the ICR where the data is held. A hashing algorithm called Secure Hash Algorithm 2 with 512 bit hash values (SHA2-512) will be applied. NHS numbers and dates of birth in the RCGP RSC database are already hashed using the same algorithm. Postcodes have also been converted to LSOAs. This will facilitate the data linking process without the need of any member of the research team at the University of Surrey to access the patient identifiable information. The SHA2-512 is a cryptographic hashing algorithm approved to de-identify personal information. It uses asymmetric encryption and is described as a one-way function, which means that it is computationally impossible to generate the original data from hashed values, even with the use of the secret key used for hashing.
CHHiP data transmission

Data for 3179 UK CHHiP participants, including study ID, recruitment centre, hashed NHS numbers, hashed dates of birth, LSOAs, age, randomization group, clinical baseline information such as tumour stage, co-morbidities and medications, together with symptoms and radiotherapy-related-toxicity recorded with PROs and clinician-reported tools (see Table 2) will be transmitted to the University of Surrey and stored on a secure server. Access to data will be limited to the research team and will be password controlled.

Data linking

First, hashed NHS numbers will be used as a unique key to link the two separate databases. For patients that cannot be linked through this method, hashed dates of birth, the LSOA, and possible diagnosis of prostate cancer will be explored as a secondary link-age method. The information from the RCGP RSC records on the number and type of co-morbid cardiovascular and diabetes conditions as well as medications taken by CHHiP patients will be extracted (see Table 1).

Data analysis

To assess the value of the linked resource, statistical analysis of the effect of co-morbidities and medications on patient- and clinician-reported symptoms and radiotherapy-related toxicity will be conducted. The number of CHHiP patients with co-morbid conditions and the number and type of prescription medications that patients take will be described. Medical history collected as part of the CHHiP trial will be compared with that obtained from the RCGP RSC. To investigate the representativeness of the linked subsample, the incidence (proportion of patients with co-morbidities and medications) in the RCGP RSC linked CHHiP subsample will be compared to the overall CHHiP population and to the RCGP RSC population. The occurrence and intensity of symptoms and radiotherapy-related toxicity in the RCGP RSC linked CHHiP subsample will also be compared to the overall CHHiP population. The toxicity profiles of patients with co-morbidities and medications will be compared to those of patients that do not have specific co-morbidities or do not take medications to investigate the effect. A detailed data analysis plan is described in section ‘Data analysis’.

Data dictionary

A systematic literature review was conducted to gain understanding of which medications and co-morbidities interact with radiotherapy, and what their impact on the side-effects from radiotherapy may be. The literature review fed into the data dictionary and the RCGP RSC extraction query will be based on knowledge gathered during the literature review and consultations with clinicians. The data extraction will be defined as follows:

Co-morbidities and symptoms

The ontology was developed to extract the relevant co-morbidities and symptoms from the RCGP database for CHHiP patients. This allowed a conceptual map of symptoms, investigations, administrative codes, and diagnoses that can indicate a case to be built [45]. For instance, a person with diabetes may not always have a clear diagnosis code in the GP record, but they might have administrative codes (diabetes review) or investigation codes (HbA1c blood test results indicating diabetes), from which it can be inferred that the patient is a diabetes case.

Medications

A list of relevant medications was created based on sections 2 and 6.1 (Drugs related to cardiovascular system and diabetes) of the British National Formulary (BNF) (www.bnf.org). In the same way as for co-morbidities and symptoms, the list of medications was first developed, and then the list of related codes required for data extraction was derived.

Statistical analysis

Standard descriptive statistics will be used to review the number of co-morbid conditions and prescription medications of CHHiP patients for which RCGP RSC data are available. Baseline information on co-morbidities and medications recoded in CHHiP will be used to analyse the concurrence between the two data sources. The McNemar test for paired data as well as proportional odds logistic regression will be used to assess statistical significance of
the difference between co-morbidities reported in CHHiP and those revealed in RCGP RSC data. A chi-squared ($\chi^2$) test will be used to compare the incidence (proportions) of co-morbidities in the RCGP RSC linked CHHiP subsample and in the overall CHHiP sample and RCGP RSC population.

Using the information on symptoms and radiotherapy-related toxicity recorded in CHHiP, the occurrence and intensity in the overall CHHiP population and in the RCGP RSC linked subsample will be described. The homogeneity of the RCGP RSC linked CHHiP subsample will be assessed with a $\chi^2$ test. Logistic regression will be applied to relate the information on occurrence and intensity of symptoms and radiotherapy-related toxicity to co-morbidities and prescription medications. This will be done to investigate the effect of co-morbidities and medications on symptoms and toxicity. The levels of symptoms and toxicity will be summarised for people with particular co-morbid conditions. This information will be compared to people without co-morbidities and to the general CHHiP population to assess if patients with co-morbidities have higher or lower toxicity levels. Information on particular medications such as statins or ACE-inhibitors taken by patients before, during and after radiotherapy will be used to investigate the effect of these medications on symptoms and toxicity. The information on each of the medications (by a pharmacological group) will be used as a binary item in the logistic regression. The plan of data analysis is illustrated in Fig. 1.

Age is a well recognized confounding factor [2,46], and therefore the modelling of radiotherapy-related symptoms and toxicity will be adjusted for age. The regression analysis will also be adjusted for the effect of the CHHiP randomisation group. Methods based on multilevel analysis of variance (ANOVA) will be used to model the effect of co-morbidities and medications on the development of symptoms and toxicity over time. Those methods provide a variance split in the data according to the contribution of experimental factors [47]. The effect of co-morbidities or medications over time will be isolated and assessed without confounding factors such as age or randomisation group. If feasible and accordingly to the success of data linkage, Generalized Estimating Equations (GEE) [48] will also be used. This is an approach developed for the longitudinal nested data. It allows for the inclusion of categorical as well as continuous variables and for variable selection procedures in order to select the best model [49]. Regression parameters can be calculated for each point in time. Therefore the effect of co-morbidities and medications on acute symptoms can be compared to that on long-term effects.

**Discussion**

EBRT can lead to functional and structural damage that can cause long-term symptoms. The accumulation of radiation in the tissues results in DNA damage and changes in the cellular micro-environment, mainly via cytokines-inflammatory pathways. The process of cell reparation and restoration is similar to that of wound healing [50]. However, repetitive injury during the course of radiation can lead to scaring which in the long-term manifests as fibrosis, atrophy and vascular damage [51,52]. Potential cellular and vascular changes that impact on the side-effects from radiotherapy are not fully explained. The evidence regarding the effect of co-morbidities and medications on acute and long-term effects is also conflicting but some studies suggest that concomitant medications may affect the inflammatory response induced by radiotherapy. Cardiovascular medications change inflammatory responses and microvasculature and it is believed that through these mechanisms they impact on radiation toxicity [29,33].
Long-term injury from EBRT is a serious concern often limiting treatment. Fibrosis reduces the elasticity and vascularisation of tissues and organs such as the bladder or bowel, and this leads to lasting side-effects [53–56]. Research shows that the occurrence and severity of long-term side-effects depends on multiple treatment factors such as the type of treatment, radiation total dose, dose per fraction [17,57–59] and the type of irradiated tissue [60,61]. Late side-effects are associated with age, baseline patient characteristics and intensity of baseline symptoms and short-term side-effects. Recent studies also recognised mechanisms of genetic risk factors [62]. In addition, patients with co-morbid conditions are at a higher risk than others [63–65]. Risk of fibrosis is higher in patients with hypertension or diabetes due to changes in microvasculature, or with scleroderma due to collagen over expression [66]. Despite our increasing knowledge of these risk factors, it is still difficult to predict the occurrence of fibrosis and late-effects in patients. However, exploring co-morbidities and medication use may be of benefit because of the role that they play during regenerative processes and the effect on inflammation, microvascular damage, or hypoxia.

The research into the risk factors has produced conflicting evidence but some studies show that cardiovascular medications taken by patients to control their co-morbidities may reduce radiotherapy-related toxicity [21,23,24]. The mechanisms are not fully established but it is believed that improving the microvascular flow of the healthy tissue surrounding tumours may reduce the inflammatory response that is responsible for many of the side-effects, and so those medications may protect against normal tissue injury caused by radiation. The evidence to support this association is limited and there is a need for more research.

Data linkage techniques are increasingly being used to create comprehensive datasets that can be used to explore specific issues or search for evidence that could not be investigated in the limited data available from isolated studies. Despite the clear potential and increasing patient benefit, this type of research is still hampered by serious governance and data protection issues. To address patient confidentiality concerns, an established method of data linkage has been used. This method has been deemed adequate by the NHS Research Ethics Committee who approved the project. Inevitably NHS numbers are required for linking large datasets such the two used in this study. However, the method of irreversible hashing of NHS numbers that will be applied here, protects patients’ privacy while at the same time allowing for effective data linkage. Facilitating data sharing across healthcare settings and data linkage across sources is maximised and that the evidence derived from the linked resources is reliable, we need to better understand the requirements and implications of data linkage. This project will contribute to the knowledge providing the evidence with regard to risks and benefits of linking clinical trials and GP data. The process of GP data extraction will be tested and an insight generated on how this combined resource could be used to supplement information collected within clinical trials.

Conclusions

GP records will be extracted for CHHiP patients to investigate the effect of co-morbidities and prescription medications on the development of symptoms and on radiotherapy outcomes. This is a truly current approach as in the past the research mainly focused on exploring treatment factors and baseline patient characteristics. At present there is only limited evidence on the effect of medications taken for co-morbid conditions in cancer patients. Methods of reducing side-effects of radiotherapy by pharmacologically protecting normal tissue against damage from radiation have not yet been extensively explored.

The reduction of treatment side-effects has become a key challenge in modern radiotherapy as patients survive many years post treatment. The population of cancer patients is ageing and the complexity of risk factors for radiotherapy-related side-effects increases due to the high prevalence of multi-morbidity. Therefore investigating the effect that co-morbidities and medications taken during radiotherapy may have on radiotherapy-related toxicity requires more research. This research is of high relevance to patients and could potentially lead to improved health-related outcomes post-radiotherapy. To optimise the management of people treated with radiotherapy an understanding is required of how to account for multi-morbidity and its effect during treatment planning and recovery.

Conflict of interests

DD is a consultant clinical oncologist, London. DD has attended, and received honoraria for advisory boards and served as a consultant for Takeda, Amgen, Astellas, Sandoz and Janssen Pharma. Abiraterone acetate was developed at the ICR, which therefore has a commercial interest in the development of this agent. DD is on the Institute’s Rewards to Inventors list for abiraterone acetate.

All other authors declare no conflict of interests.

Funding

This work was supported by the Pump Priming programme from the Faculty of Health and Medical Sciences, University of Surrey.

Acknowledgements

We thank the RCGP RSC participating GP practices and patients for providing data. We thank patients, oncologists, urologists, radiographers, physicists and other support staff of the CHHiP trial.
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