Research article

CLINICAL INVESTIGATION

Centralized management of clinical trial feasibility requests: a single center database analysis from 2008 to 2015

Abstract

Title: Centralized management of clinical trial feasibility requests: a single center database analysis from 2008 to 2015.

Background: Evaluation of new investigational therapies requires collaborative approaches, which include industry sponsors, contract research organizations (CROs), academic research groups as well as hospital-based clinical trial units (CTUs). However, interfaces between stakeholders in clinical research are usually not standardized and lack efficiency. Research institutions are currently building up structures for mutual identification of suitable partners in the execution of clinical trials.

Methods and findings: The Clinical Trials Centre Cologne (CTCC) is a core facility of the University Hospital of Cologne (UHC) interacting with patient-near departmental CTUs, which participate in clinical trials. The CTCC set up a workflow for centralized management of clinical study feasibility requests. We collected and analyzed feasibility data from 2008 to 2015 to evaluate the concept.

The CTCC received 938 requests from 83 institutions. Duration of processing of requests was a median six days (0-148). CTCC forwarded requests to 30 discipline-specific CTUs within the UHC.

A super additive number of 1,022 assessments were performed due to forwarding to multiple potentially interested CTUs. Feasibility assessments resulted in 542 (53.0%) accepted offers, 403 (39.4%) were declined and 77 (7.5%) were not answered. Offers were declined because not enough patients were expected (125, 31.0%), CTUs conducted a competing study (70, 17.4%), study design was not accepted (56, 13.9%), insufficient resources were available (40, 9.9%), trial was not feasible within clinical routine (8, 2.0%), insufficient information about trial was given (2, 0.5%). For 102 (25.3%) declined offers, no reason was given.

Conclusions: Our data indicate that centralized feasibility management might be an effective interface in collaborative clinical research. Application to national or international networks may avoid redundant processes and enable successful trial acquisition and site selection.

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Abbreviations

CRO: Contract Research Organization; CTCC: Clinical Trials Centre Cologne; CTU: Clinical Trial Unit; IQR: Interquartile Range; UHC: University Hospital of Cologne

Introduction

To an increasing extent, clinical research has become an important aspect of the work of clinical physicians around the globe, as it constitutes an opportunity to contribute to improvement of health care and offer patients access to the most innovative medicine [1,2]. Industry sponsors, contract research organizations (CROs) and academic groups who develop and test new therapies depend on access to patients willing to participate in clinical research [3]. They need to collaborate with experts in specific fields who provide professional infrastructures for patient-based trial conduct [4]. Clinical trial units (CTUs) led by investigators in clinical departments offer such an infrastructure [5].

However, interfaces between stakeholders in clinical research are usually not standardized [6]. The missing structure for collaboration often leads to an exhaustive search for suitable sites, inefficient conduct and impaired recruitment [7].

Therefore, academic trial centers and CROs are currently building up structures for mutual identification of suitable partners in the execution of clinical trials. CROs are advocating programs for more efficient site selection and site start-up processes, aiming at single point of contacts within large medical centers [8]. Academic clinical trial centers in Germany are developing methods to enhance efficiency in administrative processes across clinical departments [9]. To our knowledge, results on these efforts have not yet been published. We hypothesized that a retrospective monocentric analysis of data on study feasibility requests framing a period of 7 years supports feasibility and usefulness of structured collaboration in site selection via centralized trial management.

Methods

The clinical trials center cologne

The University Hospital Cologne (UHC) is a 1,400-bed tertiary care institution with 34 clinical departments. The University of Cologne and the UHC incorporate a dedicated clinical research infrastructure. In 2002, the Clinical Trials Center Cologne (CTCC) was established to foster trial planning and management. It serves as a core facility with cross-sectional tasks interacting with patient-near departmental CTUs. Throughout the UHC, >350 employees are directly involved in the conduct of clinical studies as investigators or study coordinators.

Research activities include investigator-initiated trials that originate directly from unmet medical needs becoming evident in clinical practice, or emanate from basic research performed in the laboratories of the university. In addition, CTUs participate in clinical trials offered by CROs, industry sponsors (i.e. manufacturers of drugs or medical devices), or academia.

The CTCC acts as a central management and communication hub between companies and clinical experts. It structures the flow of information to identify and connect associated partners, and offers centralized management of feasibility requests searching for capable CTUs for a clinical trial. We collected and analyzed feasibility data from 2008 to 2015 to evaluate the development and benefits of this concept.

Workflow

The CTCC strategy for workflow for a centralized management and tracking of clinical study feasibility requests was set up in 2008. Two types of requests can be processed using this workflow: requests can refer to clinical trials that are ready to be initiated; others are preliminary requests sent by CROs who are in current competition to acquire the conduct of the trial.

The workflow to manage, track and document all feasibility requests is illustrated in Figure 1. The study nurses of the CTCC, who conduct trials in various CTUs within and outside of the UHC, manage the requests. The illustrated procedure shows conditional steps for co-operating sites. The CTCC interacts with other hospitals through regional and national networks. Hospitals with dedicated CTUs willing to receive feasibility requests are documented with their specific expertise. CTCC enters into general confidentiality agreements with companies sending requests frequently and with partner CTUs. Regular meetings are conducted with high frequency CROs to reconcile information on status of requests and site initiations. CTCC offers investigators partial completion of feasibility questionnaires as far as data are known.

Documentation

A feasibility blue sheet has been developed as an Excel™ spreadsheet to document relevant data on requests [10]. Data include dates of: receipt of request; forwarding to investigator; receipt of CTU feedback; and final feedback to requester. Available title and trial identifiers from requester are documented as well as requesting company and receiving investigators. The blue sheet also contains the response of the CTU regarding whether or not the offered trial is considered feasible and why. Documented data is shown in Figure 1. If a CTU is interested in participation but lacks

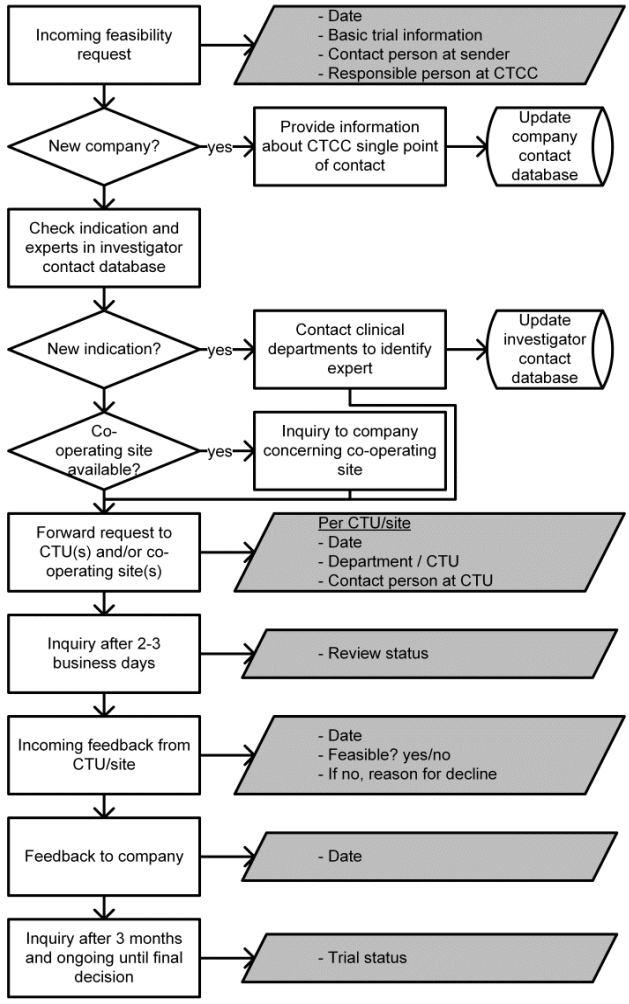

Figure 1. Workflow to manage, track and document feasibility requests addressed to the Clinical Trials Center Cologne
Companies referred to in the flowchart include contract research organization, industry sponsors and academia. Gray-colored boxes show the data that is documented in the feasibility blue sheet.
CTCC: Clinical Trials Center Cologne
CTU: Clinical Trial Unit

necessary resources, CTCC offers to provide study coordination by their study nurses to ensure adequate workforce. A missing response from a CTU is followed-up if set timelines by the requester allow for delayed response. For trials with positive response, CTCC reconciles with the institution or CTU to determine whether or not the trial has been initiated and why. Detailed data on forwarded requests to co-operating hospitals has not been documented consistently due to an increase of partners and split responsibilities between departments. Therefore, data about collaboration in the present work is confined to results regarding whether a trial has been forwarded externally or not.

The feasibility blue sheet was developed over time and via use in daily practice; it contains several free text and comment fields. These have been cleaned in the course of this evaluation to allow a structured analysis, rephrasing free text into categories.

Evaluation

Descriptive statistics have been applied using Stata™ [11]. Categorical variables are described in frequency distributions and relative frequencies, grouped frequencies were used to show development over time. For continuous variables, distribution is shown by median, interquartile range (IQR) and range. Box plot graphs illustrate distribution and outliers.

Results

From March 21, 2008 to March 31, 2015 the CTCC received 938 requests for clinical trial feasibility evaluation from 83 institutions, including 50 CROs, 22 industry sponsors and 11 academic institutions and networks. For 2009 to 2014, the median of yearly requests was 118 (IQR 113-160, range 100-165); years 2008 and 2015 are excluded, as only partially covered by the observation period.

The number of requests per sending institution had a median of one (IQR 1-4, range 1-394). With 394 requests, 42.0% of all offers were received from the most active sender, 788 (84.0%) from the 10 most frequent senders, all of those being CROs. All CROs combined sent the majority of requests (889, 94.8%), industry sponsors sent 33 (3.5%) and academic institutions sent 16 (1.7%). Time from receipt of request until final feedback was documented for 930 requests with a median of six calendar days (IQR 2-12, range 0-148) (Figure 2).

CTCC forwarded the requests to 30 discipline-specific CTUs within the UHC. A total of 531 (57.0%) offered trials were assessed as feasible. Table 1 shows the outcome of requests in regards to the successful initiation of the trial at the site. When a request did not result in a local trial initiation, the reason was also documented, if communicated.

Requests applicable to multiple disciplines were forwarded to more than one CTU. Of 48 multiple sent requests, 36 were forwarded to two CTUs, five to three, four to four, one to five and two were sent to seven CTUs. Thus, the number of feasibility assessments at the CTUs amounts to 1,022. Of these, 550 (53.8%) were done by CTUs of internal medicine departments, 249 (24.4%) by surgical departments, 100 (9.8%) to pediatric CTUs including pediatric psychiatry, 83 (8.1%) to neurology and psychiatry, 34 (3.3%) to anesthesiology and intensive care, five (0.5%) to radiation therapy and nuclear medicine and one (0.1%) assessment was done by dentistry department. Development over time is shown in Figure 3. Table 2 shows the feasibility assessments per discipline and year. Assessments for oncology trials include a total number of 37 trials on lung cancer, performed by a specified sub-unit within the oncology CTU.

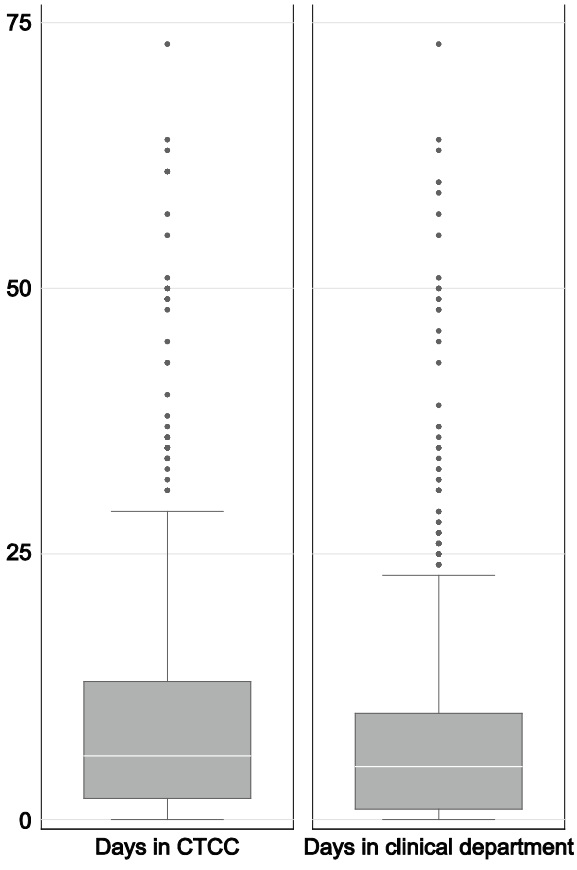

Figure 2. Duration of feedback to request

The left box plot shows the days from receipt of request until CTCC provided final feedback to the sending institution. The right box plot shows the days from forwarding of request until clinical department provided feedback to CTCC. Farest outlier in both plots is 148 days, it is not shown in the graphs to allow for better visibility.

CTCC : Clinical Trials Center Cologne

Times from forwarding of a request until CTU provided feedback to CTCC have been documented for 994 assessments with a median of five days (IQR 1-10, range 0-148), distribution is given in Figure 2. Median time per discipline ranges from 0 to 17.5 days. Requests from CROs took a median 6 days (range 0-73), from industry sponsors a median 6 days (range 0-50) and from academic institutions a median 7.5 days (range 0-148). Table 3 shows responses from CTUs regarding acceptance of offered trial participation and states the reason for declined offers.

Of 938 requests, 124 (13.2%) were also forwarded to 25 co-operating hospitals, of which 12 are located in Cologne, 11 are regional hospitals and two are national. In addition, requests regarding trials on infectious diseases were forwarded to the coordinating office of the German Centre for Infection Research, located at the university as a national hub for 14 sites throughout Germany [12].

Discussion

In our study, centralized feasibility management showed a constant flow of information between companies and CTUs in feasibility and site selection processes, possibly indicating its usefulness as an institutional interface for structured collaboration in clinical research.

The predominance of CROs in the number of companies and in the number of requests reflects sponsor practice to outsource site management of clinical trials and specifically site identification and selection [13]. Few individual CROs accounting for large numbers of feasibility requests indicate that more effort may be required to advertise centralized feasibility management.

The similar duration of response between overall response duration to company and internal duration between CTCC and CTU indicates no loss of time

Table 1. Trials initiated after positive feedback from site, estimating trial as feasible and being interested in participation.		
Trials initiated	**N**	**Percent**
Total number of feasibility requests with positive response	531	100
Trials initiated at the site	106	20.0
Trials not initiated	355	66.9
CRO not selected by sponsor	34	9.9
Trial not started	21	5.9
Declined by site after initial interest	18	5.1
Trial not conducted in Germany	16	4.5
Site not selected	15	4.2
Data missing	250	70.4
Pending	54	10.2
Data missing	16	3.0

CRO: Contract Research Organization

Table 2. Distribution of clinical trial feasibility assessments over medical disciplines from 2008 to 2015									
Medical discipline	**Total**	**2008** from Mar 21	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015** until Mar 31
Gastroenterology	**110**	11	16	15	15	8	17	26	2
Hematology	**95**	11	20	11	14	8	6	20	5
Pediatrics	**93**	13	16	8	12	10	12	16	6
Oncology	**84**	14	17	14	5	5	12	15	2
Gynecology	**72**	13	15	8	8	7	6	9	6
Rheumatology	**62**	2	8	8	10	17	4	7	6
Dermatology	**53**	4	10	9	5	6	11	8	0
Neurology	**53**	13	8	5	7	4	3	9	4
Infectious diseases	**51**	4	6	4	4	7	6	17	3
Cardiology	**43**	12	11	6	1	2	4	6	1
Endocrinology	**41**	2	6	7	5	1	8	11	1
Urology	**36**	5	6	3	6	5	5	5	1
Psychiatry	**30**	9	6	6	2	2	2	1	2
Pulmonology	**27**	4	2	0	4	2	9	6	0
Orthopedic & trauma	**26**	2	2	3	3	4	5	7	0
Nephrology	**23**	1	3	3	4	1	6	4	1
Anesthesiology	**17**	0	2	1	2	2	5	5	0
Intensive care	**17**	0	3	2	1	2	5	4	0
Abdominal surgery	**14**	3	2	2	4	2	0	1	0
Palliative medicine	**14**	3	2	5	2	1	0	1	0
Ear-nose-throat	**13**	0	3	1	2	0	0	7	0
Ophthalmology	**12**	0	1	1	2	2	3	1	2
Neurosurgery	**8**	2	3	2	0	0	0	1	0
Pediatric psychiatry	**7**	3	1	0	0	2	0	1	0
Vascular surgery	**6**	2	1	1	0	0	0	2	0
Cardiac surgery	**5**	1	0	1	0	2	1	0	0
Craniomaxillofacial surgery	**4**	1	0	1	0	0	0	2	0
Radiation therapy	**3**	0	1	0	1	0	0	1	0
Nuclear medicine	**2**	0	2	0	0	0	0	0	0
Dentistry	**1**	0	1	0	0	0	0	0	0
Total*	**1,022**	**135**	**174**	**127**	**119**	**102**	**130**	**193**	**42**

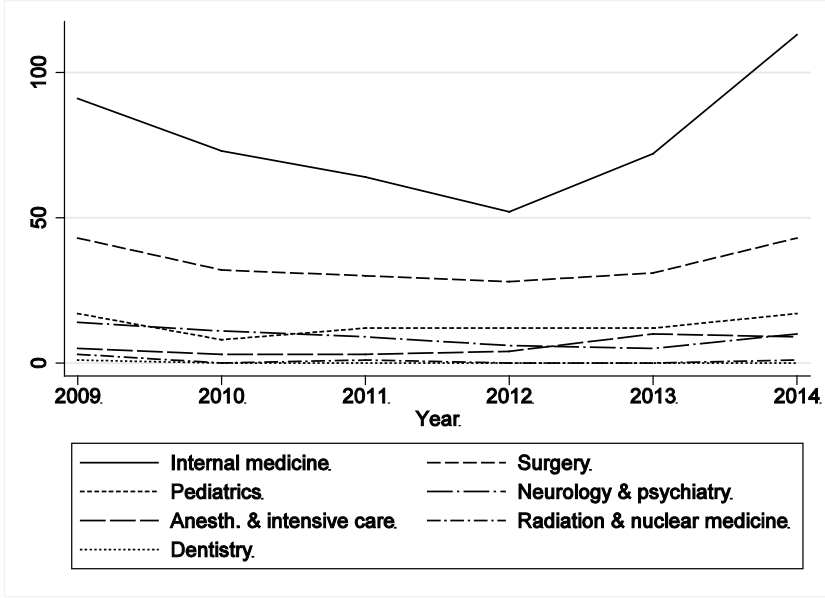

Figure 3. Development over time of sent requests per group of disciplines from 2009 to 2014.
Graph does not show years 2008 and 2015 as these have only partially been included in the observation period.

Table 3. Outcome of clinical trial feasibility assessments

Assessment of Feasibility	N	Percent
Total*	1,022	100
Accepted	542	53.0
Declined	403	39.4
Not enough patients expected	125	31.0
Competing study	70	17.4
Study design not accepted	56	13.9
Insufficient resources	40	9.9
Not feasible within clinical routine	8	2.0
Insufficient information about trial	2	0.5
No reason given	102	25.3
No answer	77	7.5
*superadditive		

through the additional step involving CTCC. In contrary, a median of six working days seems an acceptable time lapse; it would be interesting to compare this aspect of response rate with other hospitals. Missing site response was often due to strict timelines, in which the investigator was not available to respond. One CTU co-operated solely with a disease-specific feasibility network. The reasons why trials were not initiated were not stringently communicated; some institutions were unwilling to disclose negotiation outcomes, or trials were lost to follow-up after pending for considerable time.

Between 2008 and 2012, annual requests declined; beginning in 2013, requests increased. A similar trend is found for registered drug trials in Germany, if searched in the EU Clinical Trials Register, which records drug trials submitted to the competent authorities within the European Union from 2004 [14,15]. For each year from 2009-2014, we retrieved the number of trials recorded with trial status "ongoing" in Germany to assess the development over time. Apart from a general trend, the set-up of scientific research networks may have caused an increase of requests in individual disciplines. The German Center for Infection Research began applying the local concept to its national coordinating office in 2012, and from 2014, the number of requests for infectious diseases trials increased substantially. This emphasizes visibility as important selection criteria for a site or hospital [16]. Hospitals and networks may use this reciprocal effect for successful trial acquisition.

While we were able to report information over a considerable period of time and a comprehensive number of disciplines throughout a large academic center, there are inherent limitations. Our observation is limited to one hospital and region. Potential sources of variation include individual medical experts and key opinion leaders at UHC, who attract trials in their field of expertise. Commitment and performance of local personnel at CTCC and CTUs may have affected the workflow. The fact that few CROs sent the majority of requests will also have biased the distribution of trials and disciplines. Lack of a control group disables benchmarking regarding performance in the number of requests and the duration of processing. More detailed and continued follow-up might provide interesting results on time from initial request to site initiation, and potentially resulting publications. Patient enrollment numbers could obviously serve as site performance indicators [7]. However, our data forms a basis for prospective follow up research to confirm the usefulness

of centralized feasibility management and test external validity in a multicenter approach.

The emergence of the CRO industry has rekindled debate about risk and benefits in the interaction between academic and private clinical research institutions [17-20]. In addition to various opinions on how independence of research can, indeed must be retained, the need for a more efficient collaboration between stakeholders in clinical research is beyond controversy [6,20,21]. In this setting, our concept can provide an initial step in building those interoperating systems. Applied to national and international hubs imbedded into academic networks, it may avoid redundant processes for all partners. Especially in rare diseases depending on high numbers of participating investigators [3], it can also enable the active search for adequate sites and promote successful clinical trial conduct [22].

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Competing and Conflicting Interests

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Author Contributions to the Study

D.A. has contributed to the set-up and development of the described workflow and documentation. She has compiled, analyzed and interpreted data and has written the manuscript. T.S. has reviewed analysis and interpretation of data and has revised the manuscript. O.A.C. has set-up, developed and supervised the described workflow and documentation. He has contributed to the analysis and interpretation of data and has revised the manuscript.

Executive Summary

Clinical research requires the co-operation between clinical physicians and research institutions and working interfaces between these stakeholders. Single points of contact can enhance an efficient flow of information. We analyzed monocentric data over 7 years of centralized tracking of trial feasibility requests. The presented workflow shows constant communication between companies and clinical trial units that may indicate the usefulness as an institutional interface for structured collaboration. As single-center analysis, results are potentially biased and we have no long-term data on initiated trials. However, results provide a comprehensive basis for future evaluation of the concept in a prospective, multi-center approach.

Executive summary

- Clinical research requires the co-operation between clinical physicians and research institutions and working interfaces between these stakeholders. Single points of contact can enhance an efficient flow of information. We analyzed monocentric data over 7 years of centralized tracking of trial feasibility requests. The presented workflow shows constant communication between companies and clinical trial units that may indicate the usefulness as an institutional interface for structured collaboration. As single-center analysis, results are potentially biased and we have no long-term data on initiated trials. However, results provide a comprehensive basis for future evaluation of the concept in a prospective, multi-center approach.

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