



Family Physicians as Clinical Trial Investigators? - A Qualitative Study of Physicians' Experiences with a Double-Blind Clinical Trial

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Abstract

Background: Clinical (drug) trials are known as "gold standard" to provide evidence on therapy, but have rarely been undertaken in German family practices. The pilot study HWI-01 "Antibiotic vs Ibuprofen for uncomplicated urinary tract infection" was a noncommercial, double-blind clinical trial, assessing the clinical equivalence of a symptomatic treatment with ibuprofen compared to antibiotic treatment for uncomplicated urinary tract infection (UTI), and was conducted in 2007/08 according to current good clinical practice-guidelines in German family practices. Due to extensive regulatory requirements, a clinical drug trial is a great challenge for participating physicians and their teams. To optimize the planning and implementation of further randomized- controlled drug trials in a family medicine setting, views and experiences of participating family practitioners (FP) were explored subsequently in this qualitative interview study.

Methods: After close- out of the HWI-01 study, semi-structured interviews were conducted with the FPs who acted as trial investigators. The interview guideline included the areas of general motivation for participation, experience with patient recruitment as well as with study procedures in the practice. Interviews were digitally recorded and transcribed verbatim. The evaluation was carried out by content analysis.

Results/ Conclusions: Interviews were conducted with 20 family physicians in Lower Saxony, Germany. Aspects concerning physicians' motivation to participate, patient recruitment and practical aspects of trial implementation could be elucidated. For successful implementation of further clinical trials in family medicine one should consider that a) relevant study themes facilitate research participation, b) a "full waiting room" always has priority, c) procedures should be as simple as possible and d) patients expectations should be minded.

Introduction

Randomized controlled clinical (drug) trials (RCTs) are known to be the gold standard to provide evidence for therapeutic decisions. Clinical trials, particularly drug trials, have to date been rarely undertaken in German general practices. The treatment of common uncomplicated diseases such as uncomplicated urinary tract infection often lacks a good evidence base, so there is definitely a need for randomized controlled clinical trials in this setting.

The pilot study HWI-01 "Antibiotic vs Ibuprofen [treatment] for uncomplicated urinary tract infection" was the first non-commercial, double-blind clinical trial conducted in German general practices according to GCP (Good Clinical Practice), funded by the BMBF (German Ministry of Research and Education). The study assessed the clinical equivalence of a three-day symptomatic treatment with ibuprofen compared to antibiotic treatment with ciprofloxacin for uncomplicated urinary tract infection (UTI) [1].

Since the funding organization (German Federal Ministry of Education and Research, BMBF) required proof of feasibility of a double-blind drug trial in German family practice prior to funding of a full-size trial, the study had to be conducted as a pilot trial with limited sample size.

Due to extensive regulatory requirements for clinical trials, defined in the ICH-Good-Clinical-Practice-Guideline and fixed in the German Drug Law [2,3], conducting a clinical drug trial in family medicine implies a great challenge for participating physicians and their teams. In particular, sufficient patient recruitment is known to be a limiting and crucial factor in conducting trials [4].

Many studies have explored barriers and facilitators for participation in clinical trials. Lack of time and interest as well as inconvenient trial procedures during practice hours are well known obstacles to patient recruitment [4-8]. However, most of these explorative studies concerned cancer trials, mostly conducted in hospital or specialized ambulatory settings.

To optimize the preparation and implementation of further randomized- controlled drug trials concerning common illnesses in the family medicine setting, family practitioners (FP) participating in the HWI -01 trial were interviewed subsequently to the study using semi-structured interviews about their experience of participating in a double-blind clinical trial.

Aim of this interview study was to obtain information concerning the following aspects relevant for the accomplishment of clinical trials in German family medicine:

What were FPs' motivations to participate in a clinical trial?

Which experiences regarding beneficial and inhibiting factors of patient recruitment were reported?

How did the FPs and their teams consider workload by study documentation and the support given by the research team?

Methods

The HWI-01 Study

The double-blind randomized clinical trial "Ibuprofen vs Ciprofloxacin for uncomplicated urinary tract infection" (HWI-01) was conducted in 2007-2008 by the Institute of General Practice, Hannover Medical School, and the Institute of General Practice and Family Medicine, University of Göttingen. In total, 169 family practices around Hannover and Göttingen were asked to participate; 27 family practices took part as investigator sites, with 31 FPs acting as trial investigators. Most practices (n=18) were single handed – which is still quite common in Germany – and nine were small group practices with two or three FPs. However, in five group practices only one FP acted as trial investigator (Table 1).

HWI-01: Antibiotics vs. Ibuprofen for uncomplicated urinary tract infection
Pre-Study-Visit: The study was explained to all participating practices in person
Initiation visits: information, distribution of blinded medication and further material
Recruitment period: 6 months / practice, all female patients with typical UTI symptoms should be asked for participation
Monitoring visits (1-3 times during the study period): Source data synchronisation, re-check documentation / case report forms for completeness
Close out visits: after 6 months of recruitment materials and data were re-collected
Included patients: n = 79, average 2.8 / practice

Table 1: HWI-01- study scheme

The majority of the participating practices were also active as academic teaching practices for one of the University departments.

A total of 79 adult women with typical symptoms of uncomplicated UTI were included (mean 2.8 patients / practice, range 0-12). The recruitment period was six months per practice. FPs were asked to enroll all eligible UTI patients during this period, the number of six patients per practice on average was set as an objective. The overall patient recruitment of 79 female UTI patients did not quite correspond to the original expectation of a total of 100-150 patients. Thus, patient recruitment turned out to be crucial for planning further trials. Furthermore, clinical trial documentation duties according to German legal requirements [2,3] were relatively extensive compared with other studies, requiring compulsory detailed source data and adverse event documentation, possibly affecting feasibility [9].

Participants

In order to capture the subjective views of the participants in full, a qualitative study design was chosen. Following the HWI-01 study, semi-structured interviews were conducted with the FPs who took part as investigators. Interview partners were recruited until content

saturation was reached. In group practices, with one exception (FP 4 and 5) only the principal investigator was asked for an interview. In two cases the interview date was cancelled, and five FPs were not asked since content saturation seemed to be reached.

Procedures

The draft of the interview guideline was based on the experience gained in the implementation of the study, supplemented by aspects already known from the literature.

As we were interested in gaining practical experiences as a basis for further trials, the questions mainly featured the essential areas of FP's motivation for participation, of experience with patient recruitment as well as with study procedures in the practice (Table 2). All interviews were conducted face-to-face by CK in the practices. The interviews were digitally audio-recorded and transcribed verbatim.

Main topics of the interview guideline
FPs' reasons to participate in the trial
FPs' expectations concerning trial participation
Experiences with documentation, organization and support in HWI-01
Feasibility aspects with regard to daily routine surgery
Approach to patients and patients' reaction to study invitation
FPs' expectations concerning results
Sufficiency of remuneration

Table 2: Interview guideline - main topics

Analysis

Transcripts were analyzed by content analysis according to Mayring [10]. Data analysis was conducted independently by CK and JB. Initially the text was closely paraphrased; emerging topics were condensed to primary and secondary codes and matched to categories, stipulated by the guide and supplemented by new categories and subcategories. Below, they are visualized by headings, subheadings and underlining, and illustrated by original quotations.

Results

Participants

Participants (Table 3): Interviews were conducted with 20 family physicians (14 male, 6 female, mean age 45, 6 yrs). Seven FPs were working in a group practice, most FPs had single handed practices. Patient recruitment differed from 0 to 12. The final study visit (close out) had taken place 2-4 months earlier.

FP	sex	practice location	No. investigators/No. FPs per practiceurban (>100 000 inh.) rural (village/small town, <20 000 inh.)	patients recruited
FP 1	m	urban	1-Jan	2
FP 2	m	urban	1-Jan	3

FP 3	m	urban	1-Jan	3
FP 4+5	m+f	urban	2-Feb	6
FP 6	m	urban	3-Jan	6
FP 7	m	urban	1-Jan	1
FP 8	m	urban	1-Jan	3
FP 9	f	rural	1-Jan	5
FP 10	f	urban	1-Jan	1
FP 11	m	urban	1-Jan	1
FP 12	m	rural	2-Feb	6
FP 13	f	urban	2-Jan	3
FP 14	f	urban	2-Jan	3
FP 15	m	rural	1-Jan	1
FP 16	m	urban	1-Jan	0
FP 17	m	urban	1-Jan	1
FP 18	f	rural	1-Jan	3
FP 19	m	rural	1-Jan	2
FP 20	m	rural	2-Feb	12

Table 3: Sample of participating FPs

Analysis

When asked about their motivation to participate, respondents addressed issues related to the trial topic itself as well as to research in FP in general.

Retrospectively, difficulties in patient recruitment proved the major obstacle when running the trial. These occurred on an organizational level (administrative workload of obtaining informed consent, filling study documents) as well as on a personal level of the doctor (FPs had to remember the trial when unscheduled patients turned up) or characteristics of the patient (eligibility, strong opinions about the desired treatment). Highly recruiting FPs mainly worked in group practices whereas low recruiting FPs all had single-handed practices.

Accordingly, we structured the presentation of our results into the following sections:

- FPs' motivations to participate in a clinical trial
- FPs' experiences regarding patient recruitment
- Barriers for patient recruitment, reported by low recruiting FPs.
- Recruitment experiences of high recruiting FPs
- Patient perspective from FP's point of view
- Patient safety
- FPs' views on study effort and organization
- FPs' suggestions for improvement

FPs' motivations to participate in a clinical trial

The study question as to whether an uncomplicated urinary tract infection requires antibiotic treatment was considered both relevant and motivating. Many of the physicians felt that there is an excessive overuse of antibiotics. They would readily avoid the administration of antibiotics where possible and wanted more evidence for a possible change in the therapy guidelines and their own therapeutic strategies.

FP 2 "The reason is there for such a study because that would give us confidence that we can choose [a therapy without an antibiotic] really."

Moreover, studies that have the potential to directly influence medical therapy in daily routine were considered as important.

FP 5 "This practice-relevant approach...UTI is a very common condition in family medicine (...) and I found it interesting to find out whether ibuprofen works."

General interest in scientific work and in particular the cooperation with an university institution seem to be relevant motivating factors as well. Many of the FPs also actively participated in the education of medical students and had previous experience with other research projects led by academic institutes of family medicine. Very few respondents had any experience with drug trials (Table 4).

FP 4 "As we also regularly have students here, it's a little bit of a habit that we do something together with the Medical [school]."

FP 6 "...to keep in contact with academic family medicine."

Another motivating aspect was that the trial was considered a welcome addition to the routine of day-to-day practice through participation in research, in order to stay "on the ball", to explore what is new in medicine and to promote changes.

Factors reported as relevant
Relevance of the study question itself
Study setting: Family Medicine was considered superior to typical clinical trials with highly selected patients
Cooperation with academic institutions
Welcome diversification from daily routine
"Staying on the ball" concerning up-to-date treatment options

Table 4: Motivational factors for participating FPs

FP 7 "Are things necessarily right the way we do them....one should be ready to change certain habits."

Some physicians emphasized that evidence must come from the family medicine setting, as studies in hospital patients do not reflect the primary care reality.

FP 20 "And I find it's good that [studies] in family medicine also work, because I think the results are more representative of everyday life as opposed to examination of a selected patient population in the hospital clinic."

FP 11 "...good, since it [the study] is close to the base, and patients are not selected"

Others stressed the importance of independently funded research, such as our UTI study, since these studies were considered to be more

relevant than those funded by pharmaceutical companies, and expected to yield important results.

FP 9 "(...) since I think studies that are not sponsored by the pharmaceutical industry are particularly exciting."

The level of (financial) compensation was a secondary consideration for many of the respondents. However, one FP pointed out that the practices' time and labor should be included in the funding.

FP 9 "... it isn't to make money."

FP 2 "Well it's an enormous amount of time which I think practices cannot be expected to put in if they, these studies, are not funded."

FPs' experiences regarding patient recruitment

Recruitment of patients varied significantly between practices – some recruited 10 or more patients, others hardly enrolled one single woman with UTI symptoms. To provide a better overview of factors having an impact on patient recruitment we first show statements of low recruiting FPs and then those of high recruiters.

Barriers for patient recruitment, reported by low recruiting FPs

Low recruiters, as mentioned above all running single practices, repeatedly commented on the additional time required to recruit patients. UTI patients often came unannounced and the patient enrolment additionally "disrupted" the tight consultation schedule.

FP 1 (2 patients recruited) "If really under pressure all the time, when you know that in the waiting room many people are sitting there, then it's hard to do something that will take more time."

FP 7 (1 patient) "I believe that when a study takes longer than ten minutes per patient, fifteen minutes, it will be more difficult normally for a family practice."

The "barrier of the first patient" as well as long time intervals between eligible UTI-patients contributed to the fact that the practice teams' motivation to enroll patients decreased since the time-consuming inclusion procedure was perceived as a barrier, or the study already had passed out of mind.

FP 13 (3 patients) "If I had known at the beginning how easy it would ultimately be, I would not have set the bar so high for myself."

FP 19 (2 patients) "Patients always came unexpectedly, and then (...) looking for everything"

Furthermore, physicians' initial recruitment estimations were affected mainly by exclusion criteria occurring more often than expected, especially in practices treating many older patients with comorbidities.

FP 15 (1 patient)"... In such a rural practice many older patients [attend] with comorbidities and in such instances they are almost all excluded."

FP 3 (3 patients) "...since many of our older patients take antirheumatics, or have other exclusion criteria"

Some FPs admitted that they had not expected so many patients to refuse participation in the study. Refusal was mainly explained by on patients' wishes for fast symptom control and antibiotic treatment (Table 5).

Hampering factors
Time consumption
Restrictive exclusion criteria (in the UTI study: comorbid patients)
"Barrier of the first patient"
Patients do not perceive trial treatments as equivalent
Recommendations to optimize recruitment
Clear time lines and recruitment goals
Recruitment simulation training in advance of the study
Simple instructions

Table 5: Patient recruitment: hampering factors and recommendations to optimize

Recruitment experiences of high recruiting FPs

Those FPs who met the recruitment aim of at least 6 patients had in common to work in group practices. One FP reported the relevance of incentives and free trial medication for his patients.

FP 20 (12 patients) "Patients were motivated to get 10€ instead of paying 10€ practice fee...and to obtain trial medication directly from the doctor"

The only FP with clinical trial experience stated that he simply carried out his duty to fulfil the recruitment aim.

FP4 (6 patients) "I simply fulfilled the six patients, that was it."

Interestingly, one female FP running her own single handed practice recruited 5 patients without any difficulties. In this practice, many patients expressed a critical approach towards antibiotic treatment, which facilitated trial recruitment.

FP 9 (5 patients) "not to take antibiotics...that was a strong motive for patients to take part"

Patient perspective from FP's point of view

The attitude of the (potential) study participants also played a significant role in recruitment and this was at least partially dependent on their relationship with the doctor. Here, there were very different considerations that could be attributed to a wide range of doctor-patient relationships and decision-making: Some doctors said that most patients would have been quickly convinced by their doctor's recommendation to participate and by understandable and meaningful information.

FP 1 "When I think that people should do something, they generally do."

Some patients quite clearly expressed treatment expectations, in particular those with a history and experience of recurrent urinary tract infections and fast symptom resolution by antibiotic therapy. A further issue was the wish to be fit again soon, and the belief that this would better be achieved by antibiotics.

FP 5 "...since all those [patients] who have had UTIs before and knew that antibiotics help very fast, those were hard to motivate"

FP 8 "Others said: I can't allow myself this study, I have to be fit again tomorrow in any case, I want to be sure and want to have antibiotic treatment."

FP 16 (0 patients) "[patients'] demanding attitude...they expect the doctor to help immediately."

FP 8 (3 patients) "...patients with experiences from recent UTI... said "I want antibiotic treatment, that did work very well last time."

From the perspective of participating physicians, the main trial question seemed to be relevant not only for physicians, but also for patients.

FP 19 "... The context of the question - that not everything needs to be treated with antibiotics- was generally accepted [by patients] as an important issue."

FP 9 (5 patients) "not to take antibiotics...that was a strong motive for patients to take part"

Patient safety

In some cases, FPs voiced own doubts and were wary about recommending study participation to all eligible patients.

FP 18 "if somebody has heavy symptoms...then one has to overcome oneself (...) should I impose study participation on this patient?"

On the other hand, as mentioned by several FPs, patients' wants for safety seemed to be supplied by information and organizational procedures.

FP 2 "Evidently the [information] sheet was so good that they were sure that nothing could happen because all the queries and emergency exits had been anticipated."

FPs' views on study effort and organization

Due to the requirements of clinical trials, the practices' effort associated with documentation was relatively high. This was repeatedly discussed by the interviewees as "annoying" as well as "something to get used to".

FP 4 "When the paperwork is too cumbersome to edit, that's simply annoying. Because (...) it's no fun."

FP 20 "...otherwise the effort associated with all the documentation assorted with a minor medicine needs getting used to, but you do become accustomed to it."

Even monitoring visits of the study team, conducted according regulatory standards for clinical trials to assure correct documentation and to check source data, were rated differently – from "business damaging" to "good to feel supported".

FP 1 "This awful event when study records were checked for the first time (...) It took an excessive amount of time so that we decided afterwards not to go on with the study... it really was damaging our business."

FP 5 "I don't know whether these many visits are inevitable (...) I found it a little bloated."

FP 6 "For me, it was really good that someone looked at the reporting forms and said: please complete this"

For the investigators as well as the practice team, it was important that a contact person (from the study team) was reachable at any time.

FP 14 "... Always [when in touch] with the contact person, we always felt in good hands."

FP 19 "... didn't have the feeling that we disturbed the study staff with questions."

FPs' suggestions for improvement

In order to optimize patient recruitment in further studies, the FPs considered clearer timelines as useful. At the beginning (initiation visit), patient recruitment should better be simulated as an exercise to perform the procedure of patient enrolment. Easy and simple instructions for performing study-specific procedures were considered of upmost importance, as well as assistance to enable optimal integration into practice routines.

FP 7 "It must always be as foolproof as possible."

Discussion

This interview study with German family physicians who had acted as clinical trial investigators revealed valuable information regarding physicians' motivation to participate, patient recruitment and practical aspects of trial implementation. Interpreting the results, basic research and working conditions in German family medicine have to be considered:

German FPs are usually self-employed and run their practices in a system which remunerates high patient contact rates [11]. Patients have a free choice of care providers (FPs and specialists) and can change their doctor at any time.

Practice-based research networks as one may know from the US or United Kingdom [12,13] are still in the very early stage of development, and public funding for research infrastructure in primary care is still lacking.

Relevant study themes promote research participation

Many of the interviewed FPs emphasized the perceived relevance of the study theme as important for their motivation. This fits with the results of other studies on FPs' general research motivation: Askew et al. [14] described in an interview with Australian FPs that research has to be recognized both as relevant and applicable in the family medicine setting [14]. A Swiss study confirmed this, revealing a relevant topic as the most motivating factor for FPs to join in a research project [15]. - According to the interview statements of the FPs, these requirements seemed to be met by the HWI-01 study.

With regard to the field of clinical trials in family medicine in particular, Prout et al revealed benefits for patients and clinicians as main motivating factors for study participation. This was confirmed by a subsequent survey among German family physicians [16,17].

Patient recruitment: remember that "the full waiting room" always has priority

Study implementation and patient recruitment are subject to different influences. With respect to "practice routine", patient recruitment in the ongoing consultation represented a special challenge in HWI-01. It is known that trials warranting incident patient cases are often problematic [18,19].

In general, recruitment of both investigators and participants is a problematic subject in randomized controlled trials [20]. Most RCTs, independent of the trial setting, have to reconsider either the recruitment periods or the recruitment strategy. The authors of the named review again do judge the trial question of perhaps even more relevance than elaborated recruitment strategies.

With regard to our results, it seems that patient recruitment in small and single handed practices may be potentially affected more by a patient clientele with specific treatment expectations or the FP being maximally absorbed by practice routine than this might be in large group practices with several FPs and investigators.

Furthermore, in Germany supporting staff as practice manager or highly trained nurse practitioners are rather an exception and not a rule. Thus, trial management is mostly incumbent on FPs.

Research “for free” doesn’t work

Another aspect emerging from the context of study implementation in family practice is an adequate remuneration of the participating practices. Here, the German research setting has to be considered. FPs are usually busy and totally absorbed by the daily practice routine. Thus, additional time and effort spent “for free” on research activities requires a high motivation of FPs. For clinical trials, as an example, all research staff as well as all recruiting FPs must be formally GCP trained by an accredited center. Depending on the region of Germany, up to 16 hours of compulsory formal GCP training is required, constituting a considerable commitment for busy GPs [17], in particular when training means a loss of practice hours and income, combined with high fees to be paid out of pocket.

Although the FPs interviewed in this study rather underemphasized the aspect of money, the low average number of patients recruited could be interpreted as an indicator of insufficient remuneration. FPs stressed repeatedly the argument of time consumption and workload. One may suggest that these aspects would have been of minor importance, if the time spent on the study procedures would have been remunerated with the same amount as patient contacts. Obviously the current practice operation took precedence over study activities, which impacted adversely on patient recruitment and information during peak times. The “time is money” aspect has been pointed out in at least two studies from Australia and France [14,21]. The interrelation of research becoming “luxury” if not adequately reimbursed is nearly self-evident.

Consider patients expectations

Patients’ expectations of receiving antibiotics especially if already experienced with UTI were pointed out by another FP. Donovan and Parmisan mentioned in recent reports that patients’ experiences and preferences have to be considered even for trial recruitment [22,23].

Yet, none of our study FPs discussed a real critical interference with patient relationship or the feeling of endangering patients. This also may be an indirect consequence of the broad acceptance of the research question which was valued as relevant for family practice setting even by patients.

Keep study procedures simple

In line with the results from other surveys the interviewed FPs appreciated clear instructions regarding study procedures and assistance with their integration into the practice routine, as well as a

flexible and helpful study team [24,14]. Furthermore, our study as well as precedent findings showed that it is crucial to minimize trial workload as much as possible and to keep study procedures as simply as possible [25,26].

Limitations

The participating FPs in our study are clearly a positive selection of those who are generally interested in research, otherwise they would not have joined the HWI-01 study. Most were affiliated teaching practices already cooperating with one of the two university institutes. Therefore, these practices cannot be considered representative of all German FPs and results should not be generalized. However, they delineate experiences and views of a sample of German FPs interested in research, which may be particularly relevant as they constitute the subgroup of FPs who are most easily “won” for research tasks. One could assume that our FPs tended to answer in a slightly socially desirable way, because they did not want to disappoint the meanwhile somehow familiar research team. This could be a reason why we obtained relatively few answers concerning hampering factors, though patient recruitment numbers per practice were low.

Lessons learnt

Our qualitative results about German FPs’ experience with a double blind clinical trial confirm that even in a commercially competitive practice environment and with FPs who are neither research neither trained nor provided with any research infrastructure, it is possible to conduct challenging RCTs – provided that the topic is relevant and adequate support is provided.

Summing up our findings, the following aspects should be considered for successful implementation of further clinical trials in family medicine:

- Relevant study themes promote research participation
- Remember that “the full waiting room” always has priority and research “for free” doesn’t work
- Consider patients expectations
- Keep study procedures and paperwork as “fool proof” as possible

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