Influencing factors of Clinical Patient Recruitment Systems Design

Kai Heinrich
TU-Dresden
kai.heinrich@tu-dresden.de

Jonathan Philipps
TU-Dresden
jonathan.johannes.philipps@tu-dresden.de

Clinical patient recruitment (CPR) is a critical function in clinical research. However, there is no holistic design for CPR systems that incorporates functions to support all critical success factors of clinical trial performance. In order to fill this gap, a study based on a literature review and several semi-structured expert interviews was conducted. Existing theory was synthesized with newly found influence factors using categories from CPR theory and factors gathered from literature and experts. The result is a systematization of influence factors of CPR that can be used for derivation of requirements for CPR systems in a subsequent research step or for the purpose of causal modeling.

1. Introduction

Clinical Patient Recruitment (CPR) plays a major role in clinical research (CR), from which many new as well as improved therapies for patients have arisen [37]. With the growing demand on integrated health ([32]) and the usage of clinical pathways ([58]), the inclusion of patient recruitment into a holistic view of patient care due to the growing factor of patient empowerment ([13]), is a necessary step for future health care systems. Based on figures by [51] who assumed an eligibility of 420,000 to 472,000 patients for clinical trials (CT) with an oncology background in France from the period of 2006-2011, the enrolment rate for patients in CT is estimated to be 7.5 to 8.5% in 2011 versus 5.8 to 6.7% in 2003 [51]. In addition, one in five patients who were approached to enter a trial, declined. Those numbers have since then only slightly shifted upwards to an average.

Summarized, at present (calculated December 2017) there are 259,858 registered studies from 201 countries with a growth rate of 45.18% since 2000. Of these, 74.98% (45,532 of 60,725) of the open studies are waiting for eligible patients. The need of eligible patients for clinical trials grows rapidly and because of this demand, the research of CTs depends on the process and outcomes of CPR. The interviewed employees of a specific university hospital realized the necessity and value of standardized, software-based solutions to patients’ data persistence, as well as treatments with the intent to recruit patients more efficiently. However, there is a research gap between system implementations and domain influence factors in most eHealth systems [69]. The research goal of this article is therefore to offer an overview of the main factors influencing CPR systems from the perspective of different stakeholder groups. Embedded in a larger research project this goal is a necessary step towards the development of design principals that are transformed from CPR requirements. The paper is structured as follows: In the next sections, we give an overview on related fields of research involving the clinical trial recruitment process and we characterize CPR systems and their stakeholders in order to structure our results into groups that are coherent with CPR theory. In Section 3 we describe our research methods and later present the results of expert interviews and literature review in a unified framework in Section 4. In addition, we summarize those influence factors in coherence with related work in the research field of CPR to contribute to the design theory of CPR systems. Afterwards the limitations and possible improvements of our work are discussed and an outlook is given in Section 5.

2. Preliminaries and Related work

CPR describes the enrolment process concerning eligible patients for clinical trials, based on the CT protocol with their inclusion- and exclusion criteria. The related literature on the patient recruitment process can be divided into several fields of interest, according to [43]: diverse population (DV), recruitment strategies (RS), planning and management (PM), generalizability and adherence (GA), participants and physician attitudes (A) and cost of recruitment (C).

The field of diverse population is concerned with the recruitment of ethnic minorities, women or elderly. While there is no difference in the recruitment rates of elderly people, minorities are vastly underrepresented in clinical trials so far [35, 64]. Also there are rarely trials that are solely targeting the female gender [4].

Concerning recruitment strategies, it is found that there are several sources of recruitment through registries, occupational screening, direct mailing or media campaigns. While the more indirect approaches tend to have a larger reach, direct contact approaches like occupational screening have the advantage of determining key eligibility criteria on premise with less effort [27, 30, 43].
The recruitment process also needs to be planned ahead and the planning phase usually consists of different core elements like recruitment monitoring, tracking data records and staffing, especially considering the role of a recruitment coordinator [33, 62].

During the course of planning and during the execution of a CT the involved staff needs to make sure, that the study presents the qualities of adherence and generalizability. This involves adherence procedures like pre-randomization and dealing with sample stratification with regard to special subgroups that are hard to recruit [43, 67].

The remaining fields of interest that revolve around the clinical trial process are the costs of recruitment, that are very difficult to predict and the barriers to participants that result from participants and physician attitudes [43, 45].

Considering CPR systems, the main steps of CT recruitment that can be supported by an information system can be represented as a procedural model, as suggested by [9], which contains a sequence of activities, particularly: CT design, trial management and enrolling. The main goal of this model is to obtain medical knowledge based on CT results.

It is found that CTs normally do not meet their goals within the allocated time or budget, and express that CPR is to be a “condition sine qua non” for CT success. Besides, the study is not able to determine the cause of CPR obstacles [9]. A workflow example for CPR is described by [34] in more detail.

In summary, CPR consists of patient screening through predefined criteria, and the enrolment process by patient informed consent. At present, patient-screening as well as enrolment is a highly time-consuming and sophisticated process. As a consequence, computer-assisted CPR information systems are necessary, in order to improve and unclamp the barriers of the state of the art in CPR.

It is of special importance to extend the CPR influence factors to the factors that are involved in not only the recruitment phase but also the phases and stakeholder involved in the trial, to gather factors that reflect a holistic view on CPR that acts as the most essential prerequisite for building a state of the art information system for CPR [18, 22].

For the purpose of understanding the separation of the different tasks in CPR and in preparation for the literature review and expert interviews, we derived four groups which are involved in clinical research and impacting the patient recruitment process. Study designers create and plan studies with protocols, inclusion- as well as exclusion criteria [3, 63]. They are in consultation with the patient recruiter and can thus educate them. In some cases, patient recruiter contains the role of study executor, like physicians, who are responsible to perform a study’s protocols with their guidelines. The last group are study participants, which are mostly patients in the clinical area or in actual treatment, but can also be acquired externally e.g. through print advertisement [11].

We therefore structured our results in the upcoming sections based on participation groups involved in CTs: study designer, patient recruiter, study executor and study participant.

In the next section we describe our research framework and methods of data gathering.

3. Methodology

Deriving suitable requirements for engineering eHealth systems with domain specific context is crucial and literature on this topic is rather scarce [69]. Several approaches to conducting requirement engineering analysis on eHealth system have been used by [16], [8] and [66] respectively.

The common notion towards requirement engineering for eHealth systems as stated by the WHO ([77]) is to overcome the gap between domain and technology to avoid purely technology driven developments of eHealth systems, since system developed in an eHealth context differ greatly from systems used in other domains such as finance or retail [47]. [69] and [42] suggest to use a multidisciplinary approach. We therefore embed our research goal into a design science approach yielding several artifacts towards a CPR system design.

In the context of IS research the artifacts constructed by Design Science approaches often lack theoretical foundation in the form of an “analysis type” theoretical exploration, as identified by [28]. Several suggestions to this matter have been made, and it has been proposed by [29, 41, 44] to formulate domain specific influence factors as a form of design theory (DT) that creates a basis for requirements engineering and the transformation process towards design principal of an information systems, as in our case, are necessary to construct a CPR system.

In the light of the state of IS-research, we aim to present influence factors for the system domain of clinical patient recruitment as an artifact that acts as a design theory base. We already dissected the domain into different groups of stakeholders in Section 2 to create a classification system for influencing factors.

In order to avoid the above mentioned mismatch between the system and its designated domain of usage we conduct our research in a two-step approach by first identifying important influence factors from an extended literature review and secondly, by conducting several structured expert interviews to (1) ensure the found influence factors are valid and (2) to gather additional factors.

The literature review followed suggestions by [39, 71] and was initialized by conducting a search in the following databases: Google scholar, IEEE Xplore Digital Library, Springer Link, SAGE journals and Europe PMC. As a search string, we used the term “patient recruitment” in combination with “patient enrolment”, “patient screening”, “clinical trial”, “clinical decision support system”, “health management” and “patient identification system”.

Without restriction, the search yielded a total of 2,184 papers. In the next step, the results were filtered for formal criteria (research articles, free access and no
duplicates) and only articles that specifically addressed influence factors of either CPR in general or CPR systems were kept. We determined a “useful” factor by the fact that it was either transformed into a requirement in the course of the observed literature source or if it was later found to be valid by approval of the experts that were interviewed. Based on this search strategy, 378 suitable items remained.

In addition to the forward search strategy, an extensive backward search was conducted. Throughout all steps, only the approaches where the articles delivered at least some textual description of the factors and requirements affecting CPR, available with free access policy in English or German language, were taken into consideration.

We excluded 335 of the focused search results because their approaches and results did not meet those main requirements and therefore are not helpful to the cause. As a second empirical method we conducted ten semi-structured interviews.

The respondents were medical researchers, clinical patient recruiter and designer of clinical trials and therefore took on roles coherent with our theoretical findings on the CPR process in Section 2.

Seven of the interviews were conducted locally and three by phone calls using a semi-structured interview design [5, 46].

The interview partners were gathered from the institutes of oncology (4), neurology (3) and immunology (3), since those institutes conduct the most studies per year. We ensured at least one interview partner of every role per institute, as can be seen from Table 1. We decided on the somewhat weaker method of the semi-structured interview as opposed to the Delphi method, since there are rising discussions on sample sizes to ensure a proper validation of results from the Delphi method interviews, that cannot be assumed as given in our context and therefore application of the method would not be justified to a sufficient degree [2].

In addition to that, we wanted to allow for the generation of some new factors, which is more encouraged in a semi-structured setting with only top-level categories defined.

We used a structure of two main question groups: (1) we checked for coherence on existing influence factors as extracted from the literature review in a structured interview setting and (2) we asked for additional factors in a semi-structured setting. We conducted coherence checks for using the inter-coder agreement measure with regard to question group (1), specifically the percent agreement measure as suggested in [20]. A summary of the expert interview design is given in Table 1.

The interviews were recorded by audio and the results transcribed and anonymized. In order to include a specific impression of the application area of the respondent, the main influence factors for CPR were independently asked from the literature review.

Table 1. Expert Interview Setting

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Average P(k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Researchers</td>
<td>3</td>
<td>0.86</td>
</tr>
<tr>
<td>Clinical Patient Recruiters</td>
<td>4</td>
<td>0.78</td>
</tr>
<tr>
<td>Clinical Trial Designers</td>
<td>3</td>
<td>0.66</td>
</tr>
</tbody>
</table>

In addition, no specific rules were used during the interview, because the main aim was to cover additional and rules should not regiment the interviewee’s assessment and detection of new perspectives [6]. The next section presents the results of the influence factor analysis.

4. Influence Factors of CPR Systems

4.1 Empirical Results

Table 2 gives an extensive overview of influence factors with regard to subgroups relevant to stakeholder groups. It is important to state that a large part of CPR is mostly governed by pharmaceuticals and should adhere to the requirements of government agencies, which approve medicinal products for public use. Because of the heterogeneous government regulatory processes we omit this family of factors from our analysis since it is very dependent on the country the trial is conducted in.

Influence Factors not marked with at least one literature reference are factors obtained by the interviews. After conducting the literature review and the semi-structured interview setting, we identified some additional clusters that can be interpreted as concept groups according to [71]. We used subgroups like organizational specific that came up as summary concepts during the semi-structured interviews, as they were mentioned by the participants (e.g., “from an organizational point of view […]”) and were unified afterwards.

While all of the categories played a certain role in our research, we put a special focus on the analysis of technological factors in the upcoming analysis of Table 2, since our ultimate goal is to derive requirements that are later transformed into design principals for CPR systems.

The interviewed study designers criticized absent computer-assisted systems for study design and organizational support for CTs.
<table>
<thead>
<tr>
<th>group of factors</th>
<th>influencing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>study designer</strong></td>
<td>• A-priori testing of inclusion and exclusion criteria</td>
</tr>
<tr>
<td><strong>organizational specific</strong></td>
<td>• Design influenced by physician’s expectations in high recruitment rate</td>
</tr>
<tr>
<td></td>
<td>• Feedback and manual screening with regard to recruitment criteria</td>
</tr>
<tr>
<td></td>
<td>• Different platforms for CTs</td>
</tr>
<tr>
<td><strong>description specific</strong></td>
<td>• Complexity of clinical trial protocols and criteria [49]</td>
</tr>
<tr>
<td></td>
<td>• There are no study design standards</td>
</tr>
<tr>
<td><strong>patient recruiter</strong></td>
<td>• Source of learning of trial availability [75]</td>
</tr>
<tr>
<td><strong>organizational specific</strong></td>
<td>• Prior training [75]</td>
</tr>
<tr>
<td></td>
<td>• Barriers like huge size of open trials, difficult eligibility criteria, manual screening and administrative effort decrease enrolment rates [26]</td>
</tr>
<tr>
<td></td>
<td>• Algorithm-based screening is cheaper than manual screening and commonly used [48]</td>
</tr>
<tr>
<td></td>
<td>• Algorithm improves the accuracy of eligibility assessments [7, 23, 25, 48, 52, 53, 55, 65, 76]</td>
</tr>
<tr>
<td></td>
<td>• EHR facilitate the patient enrolment and decreases the used time [25, 53, 76]</td>
</tr>
<tr>
<td></td>
<td>• Decentralized, analogue and digital description of CTs with their management</td>
</tr>
<tr>
<td><strong>acquisition specific</strong></td>
<td>• Advertisement with smart online recruitment strategies increase patient recruitment [12]</td>
</tr>
<tr>
<td></td>
<td>• Success of standard therapy [75]</td>
</tr>
<tr>
<td></td>
<td>• Impression of trial’s scientific merit and toxicity [75]</td>
</tr>
<tr>
<td></td>
<td>• Facilitate the communication with potential eligibility patients and coordinators [21]</td>
</tr>
<tr>
<td></td>
<td>• Strength of recommendation [75]</td>
</tr>
<tr>
<td><strong>notification specific</strong></td>
<td>• Alert systems increase patient’s attendance [25, 49, 53, 73] and improves patient recruitment for emergency settings by agile responsiveness [36, 61]</td>
</tr>
<tr>
<td></td>
<td>• Failed notifications limited the alert system and their usage [61]</td>
</tr>
<tr>
<td></td>
<td>• Different time for data acquisition and digitization</td>
</tr>
<tr>
<td></td>
<td>• Different screening cycles for different application areas (e.g. shorter screening cycles for stroke units)</td>
</tr>
<tr>
<td><strong>data specific</strong></td>
<td>• Various data- maintenance and access</td>
</tr>
<tr>
<td></td>
<td>• Ward-specific systems for patient management</td>
</tr>
<tr>
<td></td>
<td>• Manual evaluation and search effort, because of missing patient data [72]</td>
</tr>
<tr>
<td></td>
<td>• The quality of patient recruitments through SQL statements depends on their data like the database schema [48]</td>
</tr>
<tr>
<td></td>
<td>• Specific data types like images or free-text data are difficult to examine from inclusion- and exclusion criteria [76]</td>
</tr>
<tr>
<td><strong>screening specific</strong></td>
<td>• Screening methods depends on the application area [60]</td>
</tr>
<tr>
<td></td>
<td>• EHR increase the patient recruitment rate [49, 76]</td>
</tr>
<tr>
<td></td>
<td>• Criteria should be weighted differently [50]</td>
</tr>
<tr>
<td></td>
<td>• Different knowledge about technical possibilities and existing features create bias</td>
</tr>
<tr>
<td></td>
<td>• Screening’s results have to be reviewed manually, because of incorrect assignments [65]</td>
</tr>
<tr>
<td></td>
<td>• Algorithm based screening methods enhance patient recruitment [48, 60, 65]</td>
</tr>
<tr>
<td></td>
<td>• Screening with SQL statements cause limits in precision like false positive assignments [48]</td>
</tr>
<tr>
<td></td>
<td>• Unstructured data like free text cannot be used for algorithm-based screening yet</td>
</tr>
<tr>
<td></td>
<td>• Screening depends on patient’s treatment and newly discovered diseases [14, 52]</td>
</tr>
<tr>
<td></td>
<td>• Screening results depend on Hospital Information System (HIS) data quality [23]</td>
</tr>
<tr>
<td></td>
<td>• Manual efforts for patient screening, because a full patient recruitment system is missing</td>
</tr>
<tr>
<td></td>
<td>• There exist no complete screening solutions for semi-structured data</td>
</tr>
<tr>
<td></td>
<td>• Laboratory findings are highly structured, but not standardized (missing of uniform naming, value ranges and units)</td>
</tr>
<tr>
<td></td>
<td>• Missing standards like SNOMED-CT or inconsistent usage of ICD-10</td>
</tr>
<tr>
<td></td>
<td>• Inclusion- and exclusion criteria from clinical trials are used to search in EHR, in order to recruit patients [76]</td>
</tr>
<tr>
<td></td>
<td>• Saved time and effort depends on the simplification of inclusion- and exclusion criteria [76]</td>
</tr>
<tr>
<td><strong>study executor</strong></td>
<td>• Clinical versus research perspectives [75]</td>
</tr>
<tr>
<td><strong>organizational specific</strong></td>
<td>• Impression of impact on patient relations [75]</td>
</tr>
<tr>
<td></td>
<td>• Comfort discussing uncertainty [75]</td>
</tr>
</tbody>
</table>
There are different platforms for CTs and the key element for patient recruitment are the eligibility’s definitions. Apart from the principle of good clinical praxis (GCP) there exists no design standards for studies. Furthermore, protocol’s CT is complex ([49]), for instance the inclusion- and exclusion criteria are semi-structured and managed mostly separate and without standardized methods.

The predictions of recruitment’s results through computer-based screening methods will also support the definition of eligibility criteria for CTs. In addition, study’s success depends on tested eligibility criteria. The influencing group of factors that relate patient recruiter are organizational-, acquisition-, notification-, data- and screening specific.

Nevertheless, the influencing factors of each group are associated with among each other regarding CPR. For instance, [26] describes that huge size of open trials, manual screening and administrative effort as well as difficult eligibility criteria decrease enrolment rates. Counteractively, computer-associated screening methods through algorithms enhance the patient recruitment process [48, 60, 65]. In this context, screening results depends on the quality and accessibility of clinical data, complemented interviewee. Furthermore, heterogeneous, unstructured data like free text cannot be used for algorithm-based screening and has to be time-consuming reviewed manually. However, the interview’s as well as review’s -results shows that algorithm improves the accuracy of eligibility assessments as well as reduces manual processes, but also the used time [7, 23, 25, 48, 52, 53, 56, 76].

In contrast to unstructured data and their challenges of narrative document analysis, highly structured data like laboratory findings are not always standardized and hamper patient’s screening.

Computer-assisted systems like patient’s screening can improve their results, but in contrast, the benefits and practical usage has to be evaluated. For instance, on the one hand alert systems increase patient's attendance ([25, 49, 50]) and improve patient recruitment for emergency settings by agile responsiveness ([36, 61]) and on the other hand failed notifications limited the alert system and their usage [61].

Moreover, the final eligibility’s decision and patient’s enrolment depends on the relation between study executer and -participants. For instance, the
individual, religious as well as cultural background, attitudes towards clinical studies and research influencing patient’s enrolment [49, 75].

In other cases, patients are not interested in additionally measures ([1]) or have no time for specific treatments [54]. Otherwise, lack of time and staff engagement is for instance one of the most common obstacles in emergency areas ([19]) and in clinical trials generally ([10]). In close interaction between study executor and study participant and after their enrolment, the compliance during the treatment is one of the most important influence for CT success, as was also emphasized across all interviews. [75] describe three main factors in clinical oncology research, which relate the clinical study with their recruitment results. The physician factors describe the competence regarding CT, as well as patient's handling, such as the capability to sound rational for specific studies in an enthusiastic way and in reference on patient's needs. External perceptions of studies, like in newspapers, are an essential for aiding a patient's enrolment decision into CTs.

In addition, patient factors are also defined from their ethics or cultural background. A successful enrolment process depends on the patient's disease severity and therapy's success rate. The clinical research associate (CRA) factors are specified as an important information transfer between patients and CT. CRA requires adequate time, in order to educate the patient and to honestly compare the pros and cons of CTs with the goal of assisting the patient's quality decision [75].

In Summary, recruitment results based on patients' data and their access is one of the most influencing factors in CPR. Patients’ data are heterogeneous and semi-structured, which makes patient screening more difficult and tedious.

One reason is the various data acquisition and patient management techniques used through different patient data management systems (PDMS). [70] describe the process of analogue as well as digital data acquisition and document creation in more detail.

Tools like algorithm-based methods for patient screening improves the needed time and overhead for CPR, but there are still a lot of issues to solve. With regard to the related research fields as described in

**4.2 Synthesis of results and theory**

Section 2 we summarize the influence factors with regards to those groups in order to present another theory driven view and synthesize the design theory with our findings as in Figure 1. Since the theoretical category of recruitment strategies is only matched by the recruiters, we included them in the planning and management, rather to put it up as an own category in this context.

The same was done for the cost of recruitment, since the cost controlling was found to be largely part of managing the clinical trials.

We also found that attitudes towards specific parts of the process are often times connected to certain expectations from a physician and a patient view alike.

Therefore, we renamed the group participants and physician attitudes to attitudes and expectations (AE). In summary we yield four groups of theoretical categories: diverse population (DV), planning and management (PM), generalizability and adherence (GA) and attitudes and expectations (AE). We combined these theoretical categories from with the different phases / stakeholder of the CPR process in order to give a unified representation of influence factors, that later can be used to either test causal structures and certain relationships among them or, for our purpose, of deriving requirements for CPR systems.

This allows us to maintain the multi-influence structure from an interdisciplinary point of view, resulting in the possibility that influence factors can be present across the theoretical extracted groups from Section 2, e.g., From Figure 1 we can see that the main concerns of study design and execution is to make sure the study design and description is appropriate and that inclusion and exclusion criteria are formulated and the patient’s eligibility is ensured by a patient screening process. The main concerns here, as can be summarized by literature and interview sources alike are missing standard designs, high process complexity for Design and a principal investigator role and the gap between research interest and patient care for the study Execution.

The largest block of influence factors is given by the subgroup planning and management, that is present in all phases except of course the patient’s perspective, since they are not themselves involved in managing CTs. The main factors here revolve around the study design from an economical point of view, involving cost structures and staffing, where the lack of missing standard processes for study design make the calculation of costs and staff preparations rather difficult and lead to a high degree of administrative effort, not only regarding the study design but also regarding recruitment strategies and execution.

Especially the planning and management of the recruitment process can be divided into advertisement and communication of the study, as well as recommendation effects and the patient notification processes.

These factors concur largely with theory, but in addition a larger focus is set process support in terms of
IS systems that aid the process of recruitment through database analysis and analysis of unstructured data.

We can summarize the categories GA and PM as “hard categories”, since they give us the most important information on how to support the main functions of the CPR process and therefore are most valuable when deriving requirements later.

The influence factors from the group of AE and DP are less tangible and can be seen as “soft factors”. They play a very important role in the success of study, as they include factors that influence patient attendance, like expectations or suffering level.

However, these factors should be considered indirectly within a screening system or study designs respectively when designing a system. In concurrence with theory the patient attitude towards the trial is the largest factor to influence attendance.

The attitude is made up of the suffering level as well as treatment expectations and also the patient’s altruism level that indicates whether he is willing to enroll to help others with the same disease.

5. Summary and outlook

In this paper we presented a synthesis of theory and empirical results in order to yield a theoretical basis for constructing a CPR system. We extracted influence factors in a two-step approach: first by conducting a literature review and second, by conducting semi structured interviews with important stakeholders in clinical trials. We largely confirmed the theoretical categories and the factors from the literature review with the help of the semi structured expert interview and also added some new factors to the knowledge base. We found that the focus of the influence factors shifted towards the “hard factors” that influence CPR success with the use of supporting information systems, e.g., screening systems that are able to handle unstructured data. Some shortcoming of our method can be found in the limited number of interview participants and the fact that all interview partners were located in one hospital, so we did not control for local influences. Since the interview partners were determined as being from different institutions, we could verify that we got a broad spectrum of factors, independent of the trial parameters (e.g., cancer trial vs. ALS trial parameters). However, only four institutes were selected based on study volume, so that our cross-sectional data is somewhat limited to those fields. The general overview also lacks weight vectors for every category and factors.
Since our approach was very general with no limitations towards application, weighting with sophisticated methods like Analytical Hierarchy Process (AHP) or Analytical Networking process (ANP) would not be feasible [31, 57]. Weighting should be applied at a later stage when the specific requirements are transformed into design principals [74]. In a next step within the design cycle the critical factors can be used to derive functional- and non-functional requirements [15, 24, 40] for CPR systems.

References


Trial Alert system to enhance recruitment at the point of care", AMIA ... Annual Symposium proceedings. AMIA Symposium, 2005, pp. 231–235.


