

Integrated Information Systems for Translational Medicine*

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Summary

Objectives: Translational medicine research needs a two-way information highway between ‘bedside’ and ‘bench’. Unfortunately there are still weak links between successfully integrated information roads for bench, i.e. research networks, and bedside, i.e. regional or national health information systems. The question arises, what measures have to be taken to overcome the deficiencies.

Methods: It is examined how patient care-related costs of clinical research can be separated and shared by health insurances, whether quality of patient care data is sufficient for research, how patient identity can be maintained without conflict to privacy, how care and research records can be archived, and how information systems for care and research can be integrated.

Results: Since clinical trials improve quality of care, insurers share parts of the costs. Quality of care data has to be improved by introducing minimum basic data sets. Pseudonymization solves the conflict between needs for patient identity and privacy. Archiving patient care records and research records is similar and XML and CDISC can be used. Principles of networking infrastructures for care and research still differ. They have to be bridged first and harmonized later.

Conclusions: To link information systems for care (bed) and for research (bench) needs technical infrastructures as well as economic and organizational regulations.

Keywords

Translational medicine, health information systems, research networks, patient identification, finance

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1. Introduction

The European Union has launched an “Innovative Medicines Initiative” in order to remove bottlenecks hampering the efficiency of the development of new medicines and to improve medicines for society [1]. A strategic requirement for this aim is an improvement in clinical research and translational medicine [2]. “Translational research is to test, in humans, novel therapeutic strategies developed through experimentation” and “should be regarded as a two-way road: bench to bedside and bedside to bench” [3]. Since evidence-based medicine (EBM) is to “integrate healthcare research with healthcare practice” [4], translational medicine is the very basic concept for EBM.

The road between bedside and bench depends on information exchange, i.e. communication between the related information systems. An institution’s information system is that sociotechnical subsystem of the institution, which comprises all information-processing actions as well as the associated human or technical actors in their respective information processing role [5].

Therefore the information systems related to the bedside are the hospital information systems whereas the information systems related to the bench are the information systems of research institutions like research networks, laboratories, centers for clinical trials, etc.

A lot of work has been done in recent years to construct integrative roads inside the bedside area, i.e. patient care, and the bench area, i.e. clinical research, respectively.

Focusing on patient care, we find that in many countries the driving force for health-care has recently been the trend towards better coordination and continuity of care [6]. The focus has been changed from isolated procedures in a single healthcare institution (e.g. a hospital or a general practice) to the patient-oriented care process spreading over institutional boundaries. It has been realized that inpatient care e.g. in a single hospital – and therefore a single hospital information system – does not cover all patients’ needs in medical care. Moreover health care providers and health care professionals in a region – and in many cases even worldwide – have to collaborate in order to achieve health for the patient. This will lead to a shift towards better integrated and shared care [7]. Institutional information systems, e.g. hospital information systems [8], have to collaborate respectively and form an integrated information system, i.e. the “health information system” [9, 10] (HealthIS). HealthIS have to make available

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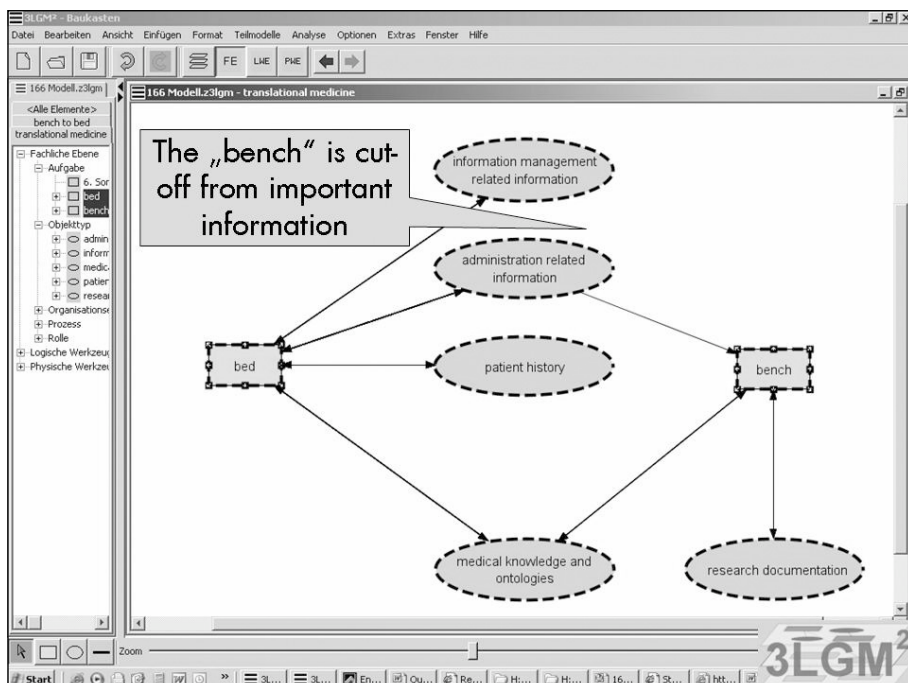


Fig. 1 Pure integration of bed and bench in the reference model for hospital information systems

not only the right information (e.g. about a patient) but also the right knowledge (e.g. about diseases and their treatment), which has to be delivered by the 'bench', i.e. by clinical research.

Nowadays, clinical research can to an increasing degree be conducted with success, and be internationally competitive, only if carried out on an interdisciplinary, often also inter-regional or international, and collaborative basis. This collaboration as well needs integrated information systems similar to those in patient care [11]. It is obvious that especially multicenter studies cannot be performed without an appropriate information system. There are a lot of solutions implemented to collect and manage data in such studies stemming from different centers. World-wide-web approaches can support remote data entry in these settings (see e.g. [12-14]). To be able not only to collect data but to support collaborative work between centers more sophisticated information systems are needed. German medical research associations have joined forces in order to work together to identify and solve related common issues and problems of a technical, legal, and organizational nature that are often unconnected with the spe-

cific clinical problem and research focus. The German TMF (Telematikplattform für Medizinische Forschungsnetze), as a meta-organization, develops means for enhancing the organization and infrastructure of medical research in interlinked structures [15].

Thus integrative roads for bench and bedside respectively have been constructed successfully or are at least under construction. Unfortunately there are still considerable deficiencies concerning the links between information systems for clinical operations and care, and those for clinical research. Perhaps this is due to the limited scope and perspective of medical informatics experts both in bench and in bedside areas. As an example one can refer to the recently published 3LGM²-based reference model [16], which describes enterprise functions in academic hospitals and the related information exchange [17]. Using the 3LGM² tool [18] all enterprise functions supporting patient care can be collapsed to form one super-ordinated function called bed and all functions supporting research can be collapsed to a super-function called bench. As can be seen in Figure 1 relationships between bench and important information like patient history are missing.

Since one of the authors of this reference model is an author of this paper too, it can be stated that the missing links have simply been forgotten due to the limited scope of the authors.

To overcome these limitations and to be able to construct the 'interstate' road between bench and bedside an interdisciplinary approach is needed. Interdisciplinarity means, that medical informatics expertise dealing with hospital or transinstitutional health information systems [19] and expertise dealing with integrated information systems for clinical trials and medical research networks have to be joined tightly.

Hence this paper deals with the question of what measures should be taken to enable the 'interstate' road as a translational two-way information road or 'information highway' between bench and bedside, i.e. the integrated information systems for translational medicine. This question has been discussed within a workshop at the 2006 annual conference of the German Association for Medical Informatics, Statistics and Epidemiology. The authors, who are physicians, health information system experts and research network experts, will give answers to the following questions:

- How to share costs of clinical trials with health insurance agencies for patient care?
- Is patient care data usable for clinical and epidemiological research?
- How can patient identities be managed in care and clinical research?
- What lessons can be learned from patient care for digital archiving of records in clinical research and vice versa?
- What are differences and similarities in secure data exchange in research networks vs. integrated care networks?

2. How to Share Costs of Clinical Trials with Health Insurance Agencies?

One of the first financial arrangements for integrated care and research has been reached for the treatment of childhood cancer. Childhood cancer is a rare disease;

the incidence in Germany is about 2000 newly diagnosed children per year. However, cancer in children applies for the most common 'natural' cause of death in this age group. The prognosis of pediatric cancer is strikingly good, three out of four children will be cured from cancer today [20]. German childhood cancer study groups play a leading role in the international concert, since childhood cancer is treated almost exclusively within clinical studies which have evolved and been optimized for almost 30 years by the German Society of Paediatric Oncology and Haematology (GPOH) [21]. More than 90% of pediatric cancer patients in Germany are enrolled in multicenter trials. The coordinating study centers of these trials usually provide both data collection and evolution of further trials besides consultation and central review of clinical findings [22]. Thereby two important aims are achieved: clinical research and best quality of clinical care. In October 2005, an integrated care network on Hodgkin's Lymphoma was started between the two existing Hodgkin's Lymphoma study groups in Germany (GPOH-HD for children and DHSG for adults) and a group of German public health insurance agencies (VdAK). For the first time health insurance partners have acknowledged that treatment according to a study protocol is the best method of quality-controlled diagnostic work-up and treatment in cancer patients.

Although the integrated care network on Hodgkin's Lymphoma is a great achievement in terms of a paradigm change towards better quality in care of cancer patients, there are still open questions to be solved [23]. Solutions are required for the coverage of reference institutions like pathology review, central review of staging and response assessment by an interdisciplinary expert team, health insurance for clinical trials, etc. Currently, new models of financing reference centers are under investigation by the associated health insurance companies, because quality-controlled treatment within a treatment optimization trial might save costs, e.g. by prevention of long-term side effects.

3. Is Patient Care Data Usable for Clinical and Epidemiological Research?

In a traditional understanding, clinical trials refer to data acquired in routine care as source documents, i.e. "all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial" [24-26]. Trial data are recorded separately, and it is the monitor's responsibility to assure that "the data required by the protocol are reported accurately on the case report forms and are consistent with the source documents". But, routine data can also be used directly in several ways for clinical and epidemiological research.

- Data may be recorded especially for a certain trial according to the related protocol but using health care information systems. If they are electronically available automatic communication to trial management systems could be provided. Standardization projects for such an interface are on the way, e.g. on an international level with a cooperation between Health Level Seven, Inc. (HL7) and The Clinical Data Interchange Standards Consortium (CDISC) [27].
- Scientific use of secondary data mainly claims data from health insurance funds. Recommendations for quality standards for secondary data analysis had been published as "good practice of secondary data analysis", addressing the whole life cycle of empirical research [28].
- Empirical research with existing routine data, e.g. for public support and pensions' research or observational studies. Because randomization of patients is not used, the effect of confounders can hardly be eliminated and may lead to erroneous interpretations of statistical correlations. Specific strategies for risk adjustment had been published [29].

The usability of patient care data depends on both the *availability* and the *quality* of data.

Availability of data can efficiently be supported by regional health information systems and the respective telematics infrastructures for health care. In Germany a telematics infrastructure for health care is now being implemented [30]. Up to now clinical research is a relatively young participant and user of the evolving platform, but the platform makes routine data in electronic patient records more and more attractive for direct utilization in medical research.

But with respect to *quality*, results of international studies reveal that a mixed use of paper-based and electronic patient records can lead to inconsistent data [31]. Questions about the accuracy and completeness of administrative data raised concerns about their use [32].

A condensed set of core record elements with credible quality and availability would be attractive for research. This basic documentation would cover only a small number of items, but would include (most of) all patients. Minimum basic data sets can for example be found for pediatric oncology [33] or for orthopedics [34]. They can be used for resource planning, reimbursement, quality control, research, and health statistics. The basic documentation widely available in Germany today is mainly defined by legislative regulations and especially the DRG system, but not a result of clinical or research requirements. Nevertheless its coverage of the whole population, which leads to information on 17 million inpatients or 700 million prescriptions, is appealing.

From the point of view of research several demands come up:

- *Availability of relevant items:* A widely accepted basic data set from routine care, which is largely independent from a specific question or study, is needed. Without this consent, the use of routine data in research projects will be due to chance alone.
- *Reliable definition of items:* Medical research needs an understandable and reliable definition of each data item that complies with international standards. There are many opponent examples, e.g. the grading of pressure ulcers in the ICD-10 that does not comply with the

grading defined by European and American scientific societies.

- *Appropriate level of data quality:* The concept of data quality must be made operationally feasible, measurable, and assessable. An initial concept has been presented defining 24 indicators for data quality, 10 in the category of plausibility, 7 in the category of organization and 7 in the category of trueness [35].
- *Unambiguous identification of objects:* Unambiguous identification is needed for each object, e.g. laboratory value, surgical procedure, referral, or patient. In Germany the latter will be reached by the introduction of a life-long health insurance number covering the whole population.
- *Legally compliant access:* On the one hand, the access to routine data should be as uncomplicated as possible. On the other hand, the rights of the citizens have to be fully guaranteed, including self-determination, disaffirmation and physical deletion of data.

Fulfilling these demands will enable an incorporation of electronically available routine data in medical research.

4. How Can Patient Identities Be Managed in Care and Clinical Research?

Patient data and samples are among the most sensitive personal information and must be carefully protected according to rules of ethics and professional discretion as well as national and international data protection laws. Thus there may be a conflict with the demand for unambiguous identification as stated just before.

In patient care we primarily have a treatment context. In this context the patient is – and should be – personally known by name. Data protection mainly follows the rules of professional discretion but also – subsidiary – the data protection laws.

However the treatment and research contexts must be separated carefully. Typical aspects of medical research are:

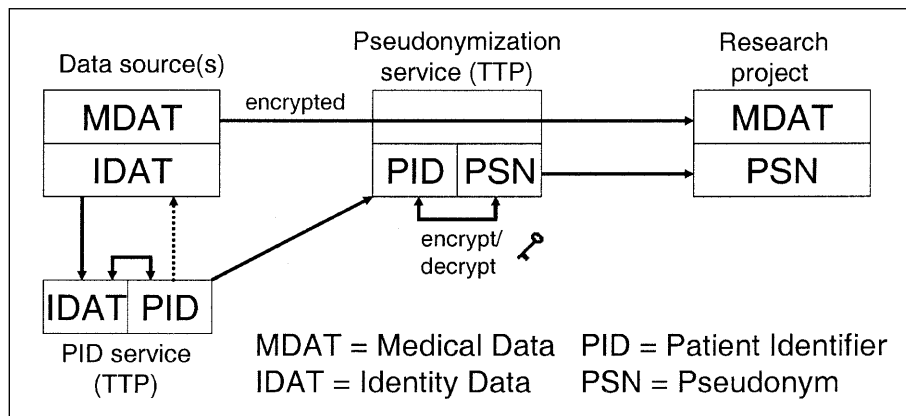


Fig. 2 Process of pseudonymization

- data leaves the treatment context for evaluation or storage, and
- identity of the patient doesn't matter, there is no direct contact.

In such a context use of anonymous data is preferred. But this doesn't always work: In many cases of medical research the correct association between a single patient's data from distinct sources or distinct points of time is crucial. In some scenarios a way back to the person is required: It could be in the interest of the patient to learn about results of a research project, for example a genetic disposition; or a researcher might want to use a data pool to recruit suitable patients for a new study. In these cases pseudonyms (aliases) are the proper concept: Replace the identifying data with a meaningless random string [36]. In "small" projects this is simply done during data export. In "large", multicenter projects – or when data or samples will be kept for a long time – the process of pseudonymization needs one or more external trusted third parties, which create unique identifiers and encrypt them to form the pseudonyms.

Figure 2 illustrates a process of pseudonymization, as it is used in a German research network [37]. It maintains a comprehensive patient list, matches personal data and creates pseudonyms (PSN) from patient identifiers (PID). The patient list consists of different database tables that contain information about each PID request such as partly encrypted input data items, the matching outcome and of course the PID itself.

The user submits a person's medical and identity data using a web interface. The PID service compares the submitted data record with those of the patient list. Depending on whether a match is found or not an existing PID is returned, a new one is generated, or an error message is displayed. At the same time, the PID database is updated with the new data. The pseudonymization service encrypts the PID to a PSN and provides the research project with the encrypted medical data and the related pseudonym PSN.

Several medical research networks already implemented these procedures as network services; results demonstrate that the process is appropriate for reliably identifying trial participants in medical research networks [37].

Thus a major part of an informational infrastructure for translational medicine is an infrastructure for pseudonymizing of patient care data.

5. What Lessons Can Be Learned from Patient Care for Digital Archiving of Records in Clinical Research and Vice Versa?

The Good Clinical Practice/Good Epidemiological Practice guidelines make arrangements for archiving data of clinical trials about ten years or more after finishing or abort [38, 39]. These trial data are generated

in electronic data capture systems, e.g. hospital information systems, mobile patient documentation, electronic data capturing, e-mail, etc. Moreover, in coordinating centers software is increasingly used for documentation, planning and patient registration. The problem of electronic archiving must therefore be solved.

In patient care digital archiving is increasingly used to archive the electronic patient records in a legally binding way [40]. The file formats used for archiving are typically TIFF or PDF, but XML is suited for archiving as well. Both PDF and XML store metadata together with the data and support digital signatures [41]. For trial data an international standard for communication and storage exists called CDISC (Clinical Data Interchange Standard Consortium) [42]. The questions are whether experiences from digital archiving in patient care can be used for archiving clinical trials and which possibilities and boundaries exist for XML- or CDISC-archiving.

From legal regulations, especially in Germany, we find that all medical parameters must be stored about a minimum of 10 years; 30 years is optimal because of limitation of actions and claims [43]. Moreover the general regulations of clinical trials make evaluation of metadata necessary. So XML and CDISC are in discussion. Experiences from digital archiving in patient care in conventional formats, e.g. from the ArchiSig-Project [43], are checked. XML can be used directly by using digital signatures or signature-containers but there are no experiences and it is rather expensive. Possibly, conversions into conventional formats are necessary, but they may not be legally harmless.

6. What Are Differences and Similarities in Secure Data Exchange in Research Networks vs. Integrated Care Networks?

For the optimization of patients' care it is basically necessary for medical centers, medical practice, chemist's shops, labs, cost

units and other partners to be able to exchange the information about a patient and his course of intersectoral treatment. Therefore secure data exchange is necessary for research networks as well as integrated care networks. Focusing on Germany, very similar approaches for secure data exchange in research networks and integrated care networks, i.e. HealthIS, can be found. Two examples may illustrate this: the German federal associations of CHI physicians (panel doctors) as well as the above mentioned TMF promote server-based architectures. Unfortunately the approaches use related but different standards and different implementations.

Within HealthIS the electronic communication in the intersectoral treatment has to support secure data exchange respecting the requirements of data protection and data integration as well as the attention of future workflows and technologies (electronic Health Card (eHC) and Health Professional Card (HPC) [30]). Furthermore, the patient data should not only be exchanged but integrated in the different communicating application systems. So the Clinical Documentation Architecture (CDA) [44] is an appropriate interchange format. As a means for the exchange of CDA-based documents the Doctor2Doctor (D2D) implementation of PaDok[®] (patient-related documentation) [45] is promoted in Germany by the associations of CHI physicians. PaDok[®] was developed by the Fraunhofer Institute for Biomedical Engineering (IBMT) and bases on a server-based architecture. This technology allows electronic communication to a known addressee, to a group of physicians or to a server-based temporary folder. In each of these scenarios the patient data will be encrypted and signed for transmission. The patient data are available on the PaDok[®]-server only with certified access authorization. Experiences e.g. in the Leipzig University Medical Center showed that using PaDok[®] needs special attention to two main problems: 1) The semantically correct data integration and 2) the compliance with security infrastructure. Because of the multitude of different software products for medical practices the implementation of PaDok[®] in medical practices has to be proven in every single case.

For research networks mere remote data entry systems are helpful [46] but not sufficient. Therefore the TMF promotes a different server-based communication system, called TMI-Server. This is a dedicated and proprietary implementation serving the special needs of exchanging image and text data between research centers in a research network. It is integrated with the process of pseudonymization as illustrated in Figure 2. The TMI-server supports the CDISC standard for describing clinical trials [42] but, of course, does not support different addressing modes as needed to support patients' liberty to choose a doctor deliberately. Another server-based approach using CDA intensively is presented in this issue [47].

Thus both the approaches for HealthIS and for research networks look very specialized for their domain. Therefore it is not appropriate to try to harmonize the two approaches. But it is reasonable to first implement bridges between the two approaches and domains.

7. Conclusion

High-quality patient care depends on translational medicine. Translational medicine needs integration of information systems in patient care and research networks.

So we can conclude first: High-quality patient care does not only need HealthIS but also information systems for research networks and their proper integration into integrated information systems for translational medicine.

The second conclusion is that integrated information systems for translational medicine aren't only based on modern and proper IT infrastructures. A bundle of arrangements from finance to IT is needed:

- If integrated information systems shall not only work for the lifetime of a project but longer, they need a solid financial basis. Since clinical trials are widely accepted as improving quality of care, insurers actually can be convinced to share parts of the costs.
- Usability of patient care data clearly depends on physical accessibility, which can be reached by means of IT. Moreover

usability depends on appropriate quality of care data. High-quality data requires more effort to introduce minimum basic data sets.

- Even research needs data with patient identity. The conflict with privacy can be solved by implementing pseudonymization services for research networks.
- Archiving patient care records and research records is similar. Thus experience in, as well as systems for, storing and archiving electronic patient records can be applied for storing research records as well. Experiences using XML and CDISC in the research domain should be applied for patient care where appropriate.
- IT infrastructures for HealthIS and research networks are implemented following similar but different principles. Harmonization doesn't seem to be appropriate today, since different requirements have to be fulfilled. Thus efforts should focus on bridging the approaches.

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