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The Standardised In-Line Clinical Case Series: A New Concept for Real-World Evidence in Dentistry

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Abstract

Clinical investigations are a crucial part of scientific research. The results can help guide clinicians in treatment decisions in their daily practice, and can pave the way for further advancement. In some fields, however, some of the more traditional types of clinical investigation have limitations that can affect not only how they are conducted but also the quality of the results obtained and their relevance and application in daily practice. Dental surgery, particularly implant dentistry and periodontology, is one such field, which is a major reason why observational studies, which can show a similar estimation of treatment effect, are more prevalent. Some of these observational studies have drawbacks in the dental surgical setting, and the inconsistent way that studies are described and labelled can lead to confusion in clinicians trying to piece together the best evidence for the treatment of their patients. The paradigm shift towards real-world evidence highlights the importance and relevance of real-world outcomes, i.e. therapeutic outcomes in a real-world setting. A standardised in-line clinical case series has been developed that is designed to provide strong real-world outcomes by taking into consideration clinical procedures and data belonging to the daily practice and implementing/documenting them in a controlled way. The approach standardises procedure, clinicians, training and workflows and allows consistent documentation and rapid dissemination of techniques, and may be a significant advance for real-world evidence in dentistry.

Keywords: Clinical studies/trials, Case series, Clinical outcomes, Evidence-based dentistry, Real-world evidence, Decision-making

Introduction

Clinical investigations are a vital part of scientific research, and the results arising from these studies can often have a substantial impact on how doctors and other practitioners use certain treatment interventions in daily practice. The main aims of performing clinical investigations are to investigate the mechanism of action of a treatment/intervention, assess the safety and/or efficacy of a treatment/intervention, compare the safety/efficacy of a new treatment/intervention against an established one, or to answer specific questions about a treatment/intervention.

Although crucially important, some of the more traditional types of clinical investigation (e.g. randomized controlled trials) have severe limitations in certain settings, such as surgical intervention techniques. This is particularly true in the dental surgical setting involving procedures such as bone grafting and reconstruction, periodontal surgery, and dental implant treatment. In implant dentistry especially, there is a lack of consensus about appropriate clinical investigations and the validity and relevance of important outcomes measurements. This is combined with a general lack of consistent guidelines and sometimes wildly varying opinions on clinical evidence levels and their relevance [1]. Clinical investigation in implant dentistry therefore brings a unique set of challenges. For example, due to the nature of the devices under investigation, placebo-controlled randomised clinical trials are impossible to perform, as are double-blind trials since the practitioners are always aware of what kind of device they are placing in the patients.

Comparative trials, assessing one type of implant device or surgical procedure against another, are also difficult to perform effectively, since practitioners may often have inherent bias towards a specific implant system or surgical intervention. Thus, new implants are rarely compared against a comparative device but against implants that have become the 'standard' type over many years. Unfortunately, this means that many trials purported to be 'controlled' are of questionable validity. Most clinical investigations in implant dentistry are therefore observational rather than comparative. However, the patient populations for these trials are often poorly and inconsistently defined. Different dental implant surgeons also use different procedures, even for the

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same type of surgical intervention and implant system; these differences may be particularly noticeable between practitioners in different countries. There is therefore a lack of consistent 'calibration' between clinicians and, while some standard classifications have been proposed in some areas, these are rarely followed in a consistent manner [2].

While the purpose of randomised controlled trials (RCTs) is often to address efficacy, observational studies are traditionally used to assess the effectiveness of an intervention in normal practice. However, in addition to RCTs being difficult to perform for surgical interventions [3,4], it has been shown that the estimation of effect obtained from both RCTs and observational studies is not significantly different, regardless of the actual study design or heterogeneity of study types [3,5]. These drawbacks were previously identified by Shwartz, et al. (2001), who proposed a risk management procedure to capture synergy between RCTs and non-experimental clinical studies [6].

In implant dentistry, therefore, observational clinical investigations might be shown to be more appropriate and the information gained can be just as valid as that from RCTs. RCTs are considered to provide the strongest clinical evidence, and allow causal inferences to be made, therefore they are ultimately required by the registration authorities (FDA, EU notified bodies, CFDA) to allow the commercialization of a device. Nevertheless, RCTs have several other disadvantages, which include a potentially high drop-out rate, ethical considerations that may constrain investigation of some clinical questions, and the fact that expert, specialist knowledge may be required to recognise clinically meaningful improvements [7]. Disparity in the level of improvement observed may also make it difficult to calculate an appropriate sample size to ensure clinically meaningful results [8]. For surgical procedures, especially, the level of clinician and institution experience for certain procedures may be low [8]. Finally, sponsorship by institutions such as hospitals, insurance companies or industry (e.g. medical device companies) can introduce an unintended bias [9].

In addition to this, different types of clinical intervention are not always referred to in a standardised way in the literature, which may lead to different definitions of the same clinical observation [9]. Some descriptions of clinical investigations can be contradictory, and the way that certain types of investigation are referred to can be misleading, especially for inexperienced clinicians [1]. Some of the terms used in the literature include: randomised controlled trials/studies; adaptive trials; non-randomised studies (e.g. interrupted time series studies); cohort studies (prospective or retrospective); case-control studies; case series studies; cross-sectional studies; ecological studies; superiority, equivalence and non-inferiority studies; crossover studies; longitudinal studies; and post-marketing (surveillance) studies [1,2,10]. Some of these terms have been used interchangeably in the literature to mean the same thing, e.g. 'cohort studies' and 'case series studies' have often been used to describe the same study design [1,2,5,11,12].

Cohort studies, where information on relevant outcomes is collected from groups of subjects over time [13,14], are considered to give the highest level of evidence among observational studies [3,11]. However, they can be expensive to perform and can take a considerable amount of time, as well as requiring a large sample size [3,14]. As with RCTs, the drop-out rate can also be high, and increases over time [3,13,15]. Selection bias may also be an issue in cohort studies, especially for any difference in outcomes between the patients who completed the study and those who dropped out [14,16]. Like cohort studies, case-control studies are designed to examine associations between exposure to risk factors and a disease or condition [3,17]. They can be relatively quick and inexpensive to perform compared to cohort studies or RCTs, but it may be more difficult to overcome potential bias and confounding factors [3,10,17]. Such studies contain a control element, but it may often be extremely challenging, if not impossible in many cases, to select both patients and a control population that are appropriately representative [3,15,17]. Case-control studies are also rarely population-based, which can limit their applicability [3,17].

While clinical investigations are as important in dentistry as in any other medical or surgical field, we can see that the more traditional types of clinical investigation can have severe limitations in this setting. Therefore, to keep pace with the rapidly changing dental surgical environment, a new approach is required that centres on patient outcomes in a real-world setting. One way to do this may be to look towards a specific type of case series. A case series study can be prospective or retrospective, and can be consecutive or non-consecutive [1,2]. Case series studies have a descriptive study design, unlike case-control studies, cohort studies and RCTs, which have an analytical study design. While they do not include comparison to a control element in the same way as RCTs, or cohort or case-control studies (Figure 1), they can be population-based and can accurately describe outcomes in a group of patients who have the same or similar diagnosis and who all receive the same intervention [1,18]. Such studies can be extremely useful to help analyse trends in patients and/or outcomes, generate hypotheses that can be used for further analytical studies, and to help plan appropriate state-of-the-art healthcare for the future [2,19]. The outcomes from a case series where standardised treatment interventions are used on patients that have the same clinical diagnosis can therefore provide valuable, concrete real-world evidence that can be applied in the clinic.

Real-World Evidence

'Real-world evidence' is an extension of the paradigm shift towards evidence-based dentistry over the last 20 years. While evidence-based dentistry acts as the connection between clinical investigations and their application in everyday dental practice, 'real-world evidence' takes this a step further by generating population-based data from a number of sources; in addition to direct evidence from the treatment of patients, these can include data from medical records, disease registries, insurance company databases (e.g. as described by Derks, et al. (2015) for effectiveness of implant therapy [20]), clinical databases (e.g. in hospitals, pharmacies, laboratories, healthcare agencies, and pharmaceutical and medical device companies), and systematically conducted patient surveys. Advances in electronic data capture and record-keeping have allowed rapid progression of this type of evidence-based approach [21,22]. In parallel with this, patients have become better informed and want to be presented with the potential advantages and disadvantages of different treatment options [22]. For the dental practitioner, evidence-based dentistry means being able to relate the treatment or outcome to their own clinical practice, which is

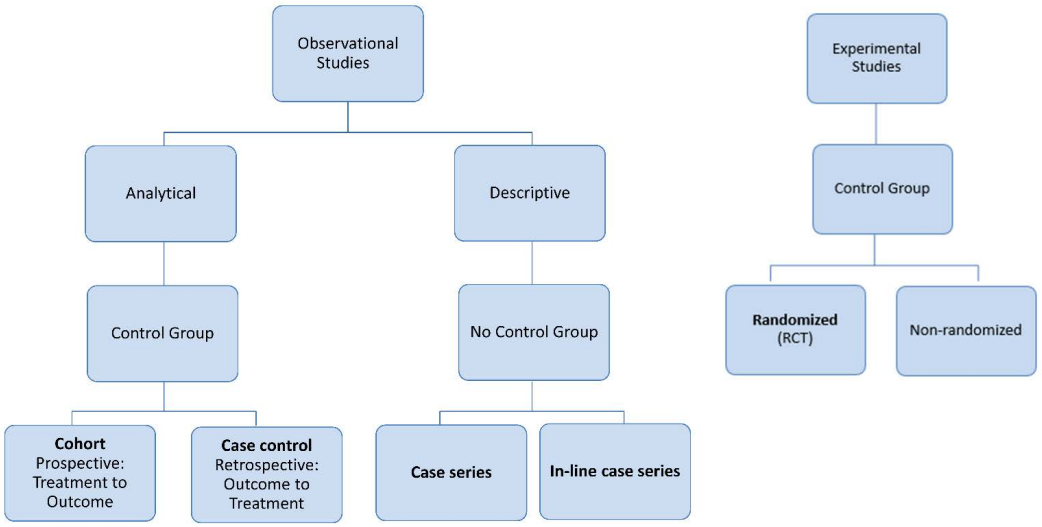

Figure 1: The main categories of experimental and observational studies, including the in-line case series concept.

much easier if the evidence comes from well conducted studies that have direct relevance to everyday clinical practice. The real-world approach allows 'real-world outcomes' to be analysed, i.e. therapeutic outcomes in patients in a real-world setting. This is particularly useful to help answer new questions more rapidly than through RCTs or cohort studies, as the data can provide a robust, longitudinal cross-section of outcomes in patients with the same diagnosis, and can highlight any potential issues with an intervention much more quickly.

A New Paradigm: The Standardised In-Line Clinical Case Series

Inspiration was taken from how preclinical *in vivo* studies are conducted in order to develop a standardised in-line clinical case series that can provide strong evidence from relevant patient populations, an aspect that is often lacking in observational clinical studies in dentistry [23]. In animal studies in the pharmaceutical and medical device industries, interventions are performed in a population with similar characteristics and take place over a limited period. In addition, the surgical/prosthetic interventions are administered in a standard fashion by operators who have been trained to a certain skill level (i.e. 'calibrated').

Patients

Patients participating in the in-line case series intervention have all been diagnosed with the same indication, for example all requiring one or more single-tooth implant reconstructions in the aesthetic zone, or requiring full-arch implant restoration in the maxilla or mandible. The patients are selected from the medical records of a clinic, or from patients who have been referred to the clinic from elsewhere; thus, there are no difficulties with patient recruitment - the patients are treated at a single location, i.e. a clinic in their city. In addition, there is often a substantial number of potential patients available with the same indication from each clinic or set of clinics in the area. This has the advantage of increasing the statistical power for measurable outcomes. In terms of defining an appropriate sample size, the criteria for success or relevant improvement should be defined and agreed by the investigators depending on the type and risk of the intervention and the combined experience of the clinicians. The sample size necessary for the defined success may then be calculated with the help of a statistician.

An agreed standard protocol is recommended for the collection of patient characteristics and follow-up data. This should include, but is not limited to, a signed participation agreement from the patient, a standardized list of patient characteristics (e.g. age, gender, date of diagnosis and/or treatment, other clinical/systemic conditions, etc). Most of these characteristics already exist in the patients' records, but should be transferred (ideally in an electronic form) to a standardized Case Report Form (CRF) relevant to the purpose of the in-line case series.

The treatment used in the in-line case series is generally the treatment the patients would have received anyway, but a higher level of quality is achieved since the procedure is standardised, minimising discrepancies or inadequacies in the technique. The patients are therefore from, and representative of, the general population; as such, inclusion and exclusion criteria, which are often based on risk factors that may have an influence on treatment in RCTs, are less strictly applied. For example, there may be a greater range of oral and systemic health status than that found in equivalent patients in an RCT. All patients with the same indication are treated at a single clinic over a short period of time. This is analogous to the three unities derived from Aristotle in classical theatre, i.e. unity of action (the same technique for the same indication), unity of time (surgery or prosthetic phase etc. occurring in a short period of time, i.e. 4 days to fully treat 30 patients), and unity of location (all procedures occurring in the same city or large clinic).

Clinicians

One of the drawbacks of RCTs involving dental implants is that the interventions are usually carried out by highly experienced dental surgeons. This creates an immediate problem for less experienced practitioners when they wish to put the

principles from certain RCTs into practice, as a specific level of skill is often required, which involves undergoing the appropriate training first. In our standardised in-line clinical case series, the operators can be a mix of general dental practitioners and expert surgeons. Our concept requires a standard training program before any intervention takes place, so that all the practitioners are 'calibrated' to the same level once they begin. One important point to note, however, is that careful selection of the clinics and clinicians is required – ideally, they should have a similar background a minimum level of general experience (5 years is recommended). Some of the clinicians may have encountered and performed some of the procedures before, but not in the same way. It is therefore important to target and profile potential clinicians as much as possible before introducing them to the in-line case series concept.

As well as the relevant clinician experience, the clinics are chosen based on area, i.e. the clinics should ideally be geographically close to each other (e.g. in the same city or region). This allows the clinicians to interact and discuss the cases and procedures, and allows a strong local support network for both clinicians and patients. For several clinics in the same place, one is designated as the lead clinic. This lead team ensures that calibration is guaranteed between the other practitioners in the area.

Training involves the whole surgical team (usually four people, consisting of one main and one secondary surgeon, one dental assistant and one person to document the whole procedure in detail) plus staff. A Team Leader is appointed for each team (usually the primary surgeon), and training is developed in collaboration with a partner (e.g. insurance company, research institution, hospital or industry). If there are several surgeons to be trained in one clinic, a detailed training plan needs to be prepared so that all the surgeons can advance to the same level before the in-line case series interventions can begin. It is important to note, however, that although training is developed together with an appropriate partner, the in-line case series are conceived as Investigator Initiated Studies, i.e. there is no sponsorship from industry or other institutions; the investigator is his own sponsor.

If there are several teams (i.e. for several clinics in a city or region), a mentor is appointed. The mentor may be a suitable experienced industry, health institution or university representative, as their job is to provide guidance on the procedures and make sure that all teams are performing the same procedures in the same way. The mentor also helps to keep the teams focused before, during and after the procedures, and ensures that communication between the teams is consistent. Importantly, the training should also include standardized data collection and subsequent data entry, so that the data can be collated for analysis quickly and easily.

The training sessions take place during the 2-3 months before beginning the in-line clinical case series protocol and involves a 'pilot phase', whereby a few patients are treated by the primary surgeon and the mentor prior to the initiation of the in-line case series. This also establishes a standard workflow and procedures. A digital CAD workflow architecture using guided surgical systems is recommended. Using such a system has the advantage of standardising the workflow between different clinics working with different dental laboratories, and of standardising the dental laboratories themselves. After the pilot phase, everyone involved in the procedure meets the day before interventions are due to begin. At this meeting, all the relevant steps in the procedure, including the surgery itself, are discussed once more, to make sure that everyone is familiar and comfortable with all stages of the process. The discussion also clarifies the expected range of time that different procedures, e.g. drilling, flap elevation, etc., are likely to take.

Logistics

Meticulous organisation is the key to success for this concept, since all patients with a particular indication are treated over a very short time span, e.g. 1 week (unity of time). This means that the patients themselves need to be present at their designated times during that week, and the clinicians' agendas need to be carefully coordinated. This organisation is important since the in-line case series interventions may be the only procedures they will be performing during that week, depending on the number of patients. All the relevant procedures and materials therefore need to be in place, and it is helpful if as much as possible can be prepared in advance, e.g. preparation of prosthodontics. In addition to coordination of the clinicians' and patients' calendars, the timing must be carefully organised in relation to the training the clinicians received, so that not too much time has elapsed. Although the medical devices scrutinized during in-line clinical case series always got previous approval from the Health Authorities (FDA 510k, CE mark, etc) patient consent must be sought in advance, and approval from the relevant Institutional Review Boards or ethical committees, depending on the country, must be in place.

Follow-up procedures also need to be standardised, which is especially important since the patients treated have the same constraints as normal patients, i.e. they are not under the same kind of follow-up obligations as in an RCT. Outcome measurements must be agreed beforehand and consistently followed in the same manner for all teams. Thorough and systematic record-keeping is therefore essential (e.g. use of standardized Documentation/ Case Report Forms). All documentation should be double-checked by the staff with the help of a Research Contract Organisation appointed by the leading team if judged necessary. The objective of this accuracy phase consists in identifying the presence of any anomalies that may need to be documented and explained. Documentation before the initiation of the procedures includes a study protocol, approved by all parties and the relevant regulatory bodies such as institutional review boards. Any amendments to the protocol, and reasons for amendments, are also carefully documented, as in standard clinical trials. Standardised CRFs, either in paper or electronic format, are also approved and agreed beforehand, and used consistently by the practitioners; as indicated, appropriate completion of the forms is part of the training. Standard forms are also used to capture the results and outcomes. The lead clinic for the study should have a working, user-friendly electronic system for data collection, and this clinic should have the responsibility for processing and analysis of the data. Where possible, a defined central data team is recommended, which should include an IT specialist, a data manager and a statistician. This team would be responsible for checking and processing the incoming data from all participants and performing requested analyses.

Advantages

This systematic in-line clinical case series approach has several advantages, not only for the clinicians and the patients, but also ultimately for the dental surgical community. Firstly, it allows the patients to be treated very efficiently in a standardised manner using state-of-the-art techniques. In the modern environment, where patients have almost unlimited access to information about their treatment and expect high standards, the potential for excellent patient satisfaction is therefore increased. For the clinicians and clinics, the concept allows them to identify a series of patients with the same indication and treat them all rapidly and consistently under controlled conditions. As the patients are representative of the general population and drawn from the clinics participating, there may be differences in, for example, oral and systemic health status, making bias and reproducibility more challenging. However, the ultimate purpose is to make the principles and concept of the in-line case series easy and reproducible rather than the studies and patient populations, since these will be dependent on the patient pool available at a particular clinic. Conversely, there is a potential real-world advantage in that the effect of the intervention can be robustly assessed against a range of oral/systemic health conditions.

The standardised documentation approach is facilitated by the unity of time principle and allows to prepare manuscripts outlining the details of the procedures and workflows, and any deviations or issues encountered, for potential publication very quickly afterwards. This allows new or improved surgical techniques to be extremely well documented in precise detail and published for the dental surgical community early on. Standardised follow-up also allows potential publication of results in a very timely manner, depending on the indication and outcome measurements used. The clinicians performing the surgery can also gain more exposure for themselves and their clinic through local media coverage once their new techniques are made public, either through publications, congress/seminar presentations and professional/social platforms. Dissemination of a new technique can therefore be rapid but still evidence-based, since it is supported by systematic, detailed documentation and follow-up.

With Institut Straumann (Basel, Switzerland) as a partner, this concept has so far been successfully initiated in 10 European countries (Austria, France, Germany, Latvia, Lithuania, Poland, Portugal, Slovenia, Spain and Switzerland) and four countries worldwide (China, South Korea, Vietnam and the USA). The first results borne from this approach, detailing placement of short implants in edentulous patients with reduced bone height, have been successfully published [24,25].

Although the concept of this approach is relatively simple, as shown by the work flow in Figure 2, all the procedures must be strictly adhered to if it is to be successful. All the clinics need to agree and ensure that all procedures are followed, including documentation and follow-up as well as the surgery itself. It would be possible for a chain of clinics to implement such a system independently, but a considerable time and resource investment is required. Because of this, and more importantly to help with the standardised technology workflow aspects of the concept that are required, support from a suitable partner (insurance company, research institution, hospital, industry, etc.) is recommended.

Conclusions

This paper describes a new concept for a standardised in-line clinical case series approach to clinical investigation and patient treatment. This approach encompasses clinician selection, training, support, and state-of-the-art techniques and workflows that allow a team of clinicians to treat patients with the same

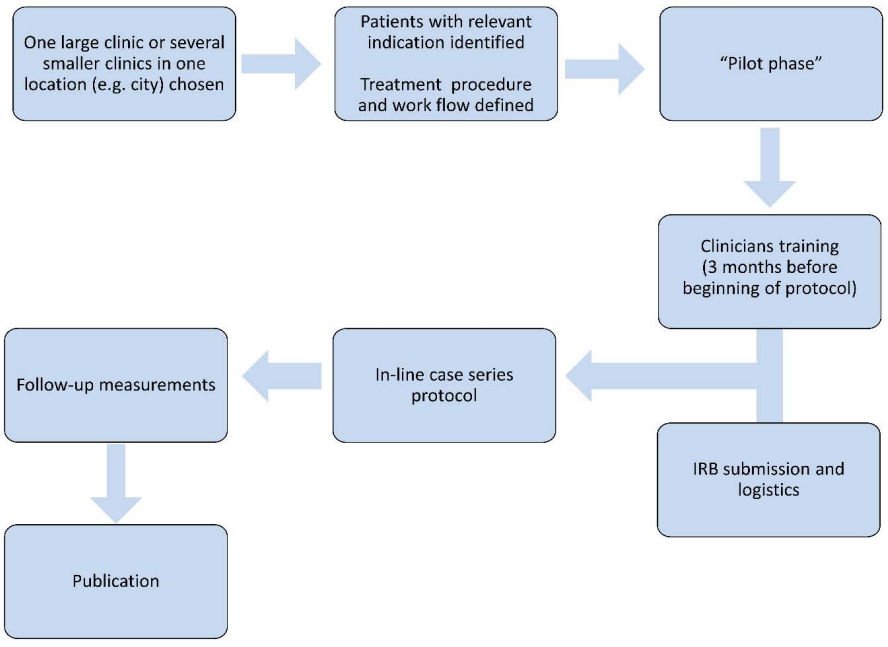

Figure 2: Work flow for standardized in-line case series.

indication in a consistent and successful manner. The approach also allows new techniques to be documented and disseminated to the dental surgical community quickly. By adding to the observational studies landscape, this approach may be extremely useful in post-registration follow-up of dental devices, interventions and treatments. This approach may be a step forward for real-world evidence in implant dentistry and dental surgery.

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Declaration of Conflicting Interests

The author declares that he is an employee of Institut Straumann, Basel, Switzerland.

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