Research & Reviews: Journal of Dental Sciences

e-ISSN: 2320-7949
p-ISSN: 2322-0090

A Novel Surrogate Parameter Measuring the Outcome in Dental Clinical Trials

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Research Article

Received: 11/01/2017
Accepted: 28/01/2017
Published: 03/02/2017

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Keywords: Surrogate parameters, Dental clinical trials, Clinical success, Clinical performance

ABSTRACT

Outcome assessment of dental clinical trials in general is either focused on survival and longevity or on highly specific parameters such as the clinical attachment level or the probing depth. However, when only a few primary objectives with limited clinical relevance are evaluated, the potential of high-quality clinical trials might not be fully exploited in terms of outcome assessment.

By combining and weighting several specific parameters, a Clinical Success Parameter (CSP) was developed as a global innovative parameter for measuring treatment success in dental clinical trials. Also biological, technical and quality of life properties in dental therapy studies can be assessed. By merging these three aspects in a combined, ideal, virtual and risk-oriented surrogate parameter, the outcome of dental clinical trials can be compared quickly, with few patients and cost-efficiently. For clinical performance evaluation, the developed CSP rating system also allows for differentiation between a large number of clinical parameters and can be focused and adapted for a wide range of specific outcome measures.

INTRODUCTION

Surrogate Parameters in Dental Clinical Trials

Clinical trials have become increasingly important in dentistry. Therefore, outcome measures of dental clinical trials should have high clinical relevance, high scientific significance and should be easily and precisely measurable. Outcome assessment in general either focuses on survival and longevity or on highly specific parameters. The latter are in most cases single surrogate parameters such as the clinical attachment level or the probing depth.

Clinical trials in restorative dentistry should last for at least five years. However, within this period of time biometric power might decline due to drop out or lost to follow-up of trial participants. For methodical reasons, clinical trials must focus on only one primary outcome measure. Highly specific primary outcome measures that are expected to show significant differences are often chosen for the outcome assessment. Caries models (e.g. hard tissue substrate, formation of a biofilm, or erosion) can be used as a surrogate for caries in clinical trials [1] and the prevalence of periapical radiolucency can be used as a surrogate for disease [2]. Surrogate parameters such as stained gingival abrasion and brushing force are utilized to assess the safety of tooth brushes [3]. Pocket probing depth, clinical attachment level and bleeding on probing are the three surrogate endpoints cited most often in the literature and are considered as measurements of clinical outcomes, i.e., surrogates of clinical events such as implant failure [4]. As far as multiple secondary measures are analysed, multiple statistical testing lowers the power of the statistical test and choosing an adequate statistical test for the given clinical situation inside the study design is a factor of great relevance. When only a few primary objectives with limited clinical relevance are evaluated, the potential of high-quality clinical trials might not be fully exploited in terms of outcome assessment.

e-ISSN: 2320-7949
p-ISSN: 2322-0090

Improvements of the patient's quality of life [5] tooth loss [6] the loss of function of implants [7] changes in clinical attachment level [8] and also histologically evidenced decay [9,10] are valid primary outcome measures used in clinical trials. Some of the highly valid primary outcome measures are limited due to invasive procedures. The selection of the primary outcome measure classifies the trial on either biological, technical or quality of life aspects. Commonly, a huge number of secondary outcome measures are investigated in order to overcome this limitation. Besides the methodology problems of this approach, the large number of parameters aggravates the comparability of different studies. Lack of standardization of the measures used for one outcome and variation in the procedures additionally complicates the comparability.

Overcoming Difficulties with Surrogate Parameters

An ideal primary outcome measure should examine a clear and convincing benefit for the patient. Selecting parameters that achieve comparable results more quickly or with fewer patients or with less cost-intensive studies therefore seems to be reasonable [11]. One possible comprehensive approach that could allow overcoming these difficulties is surrogate parameters combining several specific parameters. Therefore, the aim of this paper was to develop and apply a global parameter as an innovative procedure to measure treatment success as well as assessing dental, technical, subjective and biological properties in therapy studies in dentistry.

MATERIALS AND METHODS

Development and Application of the Clinical Success Parameter

Since there still is a lack of clinically relevant and statistically valid surrogate criteria in restorative dentistry, especially for studying new treatment procedures or products, a virtual surrogate parameter, CSP (Clinical Success Parameter), was created. The validity of surrogate parameters has been discussed predominantly in periodontology so far. The underlying trials mostly focus on the suitability of attachment loss measuring or the probing depth as a surrogate for tooth loss due to periodontal diseases [12-15].

CSP was developed by the team of authors that are specialists in the fields of clinical trials, methodology and clinical dentistry. The group was selected from different university dental schools and private dental offices involved in the conduct of clinical trials and in the assessment of methodological quality. The experts reflected critically on the CSP components and decided on the items that should be included in the new instrument. As a comprehensive expert consensus, CSP was developed to act as a predictor in respect of the correlation between clinically measurable parameters and outcome. Therefore CSP needs to cover multiple aspects and consists of the following criteria evaluating clinical performance: a) biological parameters, b) technical parameters, and c) quality of life parameters. Merging these three aspects in a combined, ideal, virtual and risk-oriented surrogate parameter, clinical trial data were selected for an exemplary application of CSP. Within the clinical trial selected, biological, technical, and quality of life data were collected. 121 patients with a fixed therapy concept received 86 temporary crowns and 35 temporary bridges during the trial. The materials used were two self-curing bis-acryl-composite resins (Luxatemp, DMG, Hamburg, Germany and Protemp 3 Garant, 3M Espe, Neuss, Germany) and a self-curing methacrylate-resin material (Dentalon plus, Heraeus Kulzer, Hanau, Germany) [16,17]. The clinical procedure was standardized and the patients were fitted with provisional crowns or bridges made of one of the three above mentioned materials during standard prosthetic treatment. This constitutes the usual procedure for treating prepared teeth. The randomized controlled clinical trial (Ethical Committee of the Medical Faculty Carl-Gustav-Carus at the Technical University of Dresden, Germany; EK75052001) was carried out in accordance with the Guidelines of Good Clinical Practice in Europe [18] and the updated Declaration of Helsinki [19]. Within the clinical trial, the findings were collected for all prepared teeth and their adjacent teeth in the course of the initial examination. On the day of the follow-up examination, the findings were recorded again. The biological (i.e. periodontal and gingival) findings were gathered at six measuring points per tooth (mesial buccal, buccal, distal buccal, mesial lingual, lingual, distal lingual) including the prepared teeth and their adjacent teeth in the course of the initial examination. All findings were recorded again before removing the temporary restoration. Pre-treatment and post-treatment scores for the plaque index (PI) according to Silness and Loe [20] the gingival index (GI) according to Loe and Silness [21] and bleeding on probing (BOP) were gathered and the changes were analysed and distributed into negative ratios (decreased plaque or bleeding), positive ratios (increased plaque or bleeding) or no changes.

The criteria encompassed by CSP as shown in **table 1** consist of different individual findings (subscores) that cover all aspects of technical, biological and quality of life properties of dental clinical trials [22,23] as well as handling parameters of the materials used. The processing and evaluation of the clinical trial data is shown in **figure 1**. The assessment was based on a system of modified CDA (California Dental Association) criteria whereas "1" is clinically flawless (very good), "3" may present minor defects that are either easily correctable or clinically insignificant (satisfactory) and "5" presents clinical defects that cannot be corrected or can be corrected only with considerable expense and requires a redo (poor) [24]. To enable the measurement and monitoring of risk, the developed surrogate parameter is determined by the poorest rating so that the poorest rating determines the overall rating within CSP processing.

e-ISSN: 2320-7949
p-ISSN: 2322-0090

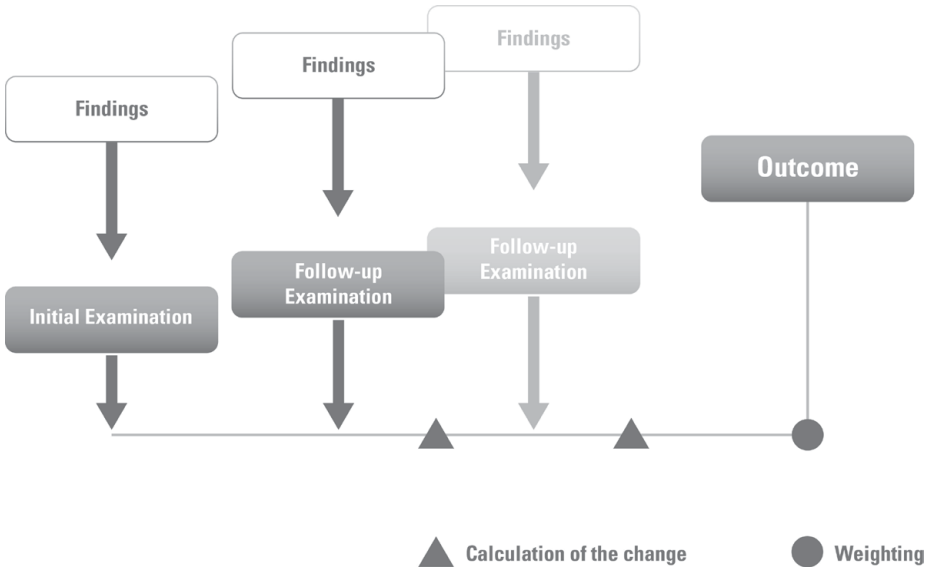

Figure 1. CSP processing and evaluation of clinical trial data.

RESULTS

CSP could be adjusted based on the underlying technical, biological and quality of life properties. The selectivity of CSP could be influenced by weighting factors (tolerance) to meet different requirements. **Table 2** shows the different weightings applied and the corresponding weighting factors: dentist weighting (CSP b), patients weighting (CSP c), technical weighting (CSP d), biological weighting (CSP e) and unweighted (CSP a). Comparing unweighted and weighted ratings of the CSP, weighted ratings result in a better average evaluation. **Figure 2** shows the unweighted CSP (CSP a) with an average of 3.4 whilst the weighted CSP (CSP b to e) improves in mean values. Taking patients and biological weighting into consideration (CSP c and e), the average evaluation value is 1.3 and 1.5. The average evaluation value worsens to 2.7 and 2.8 according to dentists and technical weighting (CSP b and d) but still remains considerably better than unweighted.

The clinical results at first (I) and second follow-up visit (II) are shown in **figure 3**. The dotted black line shows mean values of the rating scale from 1 to 5 (5=poor, 3=satisfactory, 1=very good). In terms of technical aspects, the integrity of the temporary restorations deteriorates from average 1.8 at first follow-up visit to 1.9 at second follow-up visit. Occlusal contacts improve from average 1.3 to 1.1 at second follow-up visit while there is no change in the mean value of proximal contacts. Patient satisfaction worsens from average 1.3 to 1.5 at second follow-up visit. There is also a minor decrease from 1.5 to 1.6 in the mean value of handling. In terms of biological aspects, there is an improvement in the mean value of the plaque index from 1.2 to 1.1, while there is no change in gingival index and bleeding on probing.

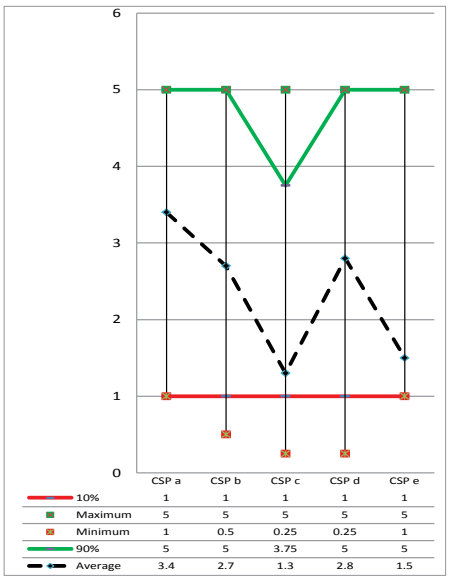

Figure 2. Comparison of unweighted and weighted ratings. CSP a: unweighted, CSP b: dentists weighting, CSP c: patients weighting, CSP d: technical weighting, CSP e: biological weighting. The dotted black line shows mean values of the rating scale from 1 to 5 (5=poor, 3=satisfactory, 1=very good). Green squares show maximum values, red squares show minimum values. Confidence interval is given by red (10%) and green (90%) lines. Weighted ratings result in a better average evaluation.

e-ISSN: 2320-7949
p-ISSN: 2322-0090

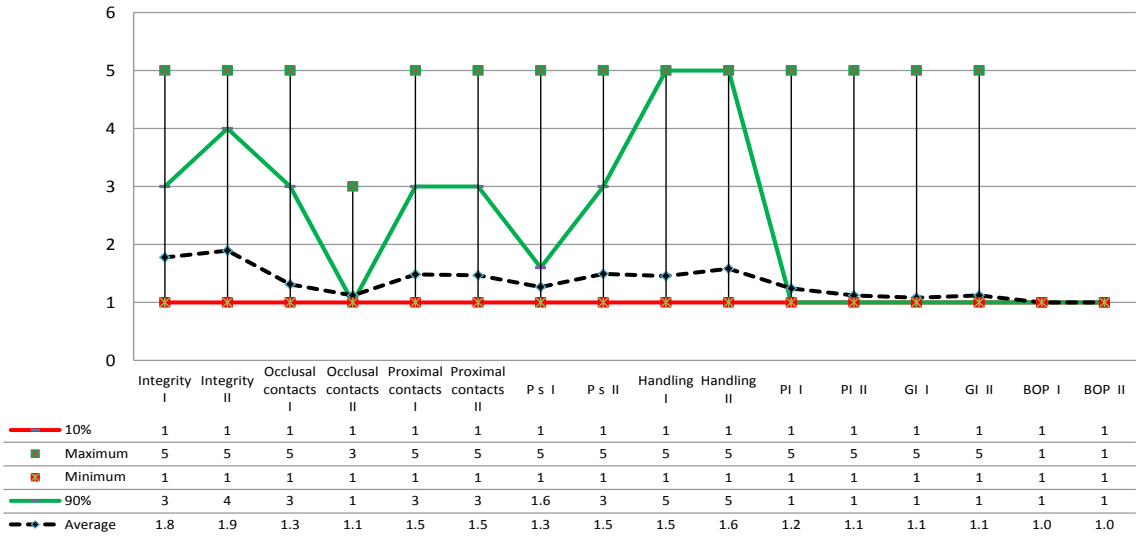

Figure 3. Clinical results at first visit (I) and follow-up visit (II): technical aspects (integrity, occlusal contacts, proximal contacts), patient satisfaction (Ps), handling, and biological aspects (plaque index (PI), gingival index (GI), bleeding on probing (BOP)). The dotted black line shows mean values of the rating scale from 1 to 5 (5=poor, 3=satisfactory, 1=very good). Green squares show maximum values, red squares show minimum values. Confidence interval is given by red (10%) and green (90%) lines.

Integrity of the temporary restoration (rated 1, 3 or 5)	
Occlusal contacts present (rated 1, 3 or 5)	
Proximal contacts present (rated 1, 3 or 5)	
Patient satisfaction on a visual analogue scale (VAS) of 0-20 On the VAS 0-6 is rated with a 5 (poor), 7-13 is rated with a 3 (satisfactory), 14-20 is rated with a 1 (very good)	
Handling Parameters	
1.	Removability of the temporary restoration after manufacturing (rated 1, 3 or 5)
2.	Adhesion in the impression material (rated 1, 3 or 5)
3.	Number of manufacturing attempts (rated 1, 3 or 5)
4.	Subjective assessment of the manufacturing procedure on a VAS of 0-20 by the treating dentist (rating: see above)
5.	Retention of the temporary restoration in the follow-up examinations (incorporated the full time: rated 1, early loss: rated 5)
6.	Removal of the temporary restoration in the follow-up examination (reincorporation possible: rated 1, fractured: rated 5)
Plaque index (PI) (rated 1, 3 or 5)	
Gingival index (GI) (rated 1, 3 or 5)	
Bleeding on probing (BOP) (rated 1, 3 or 5)	

Table 1. Criteria encompassed by the CSP.

	Integrity I	Integrity II	Occlusal contacts I	Occlusal contacts II	Proximal contacts I	Proximal contacts II	Patient satisfaction I	Patient satisfaction II	Handling I	Handling II	PI I	PI II	GI I	GI II	BOP I	BOP II
CSP a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
CSP b	1	1	0.75	0.75	0.75	0.75	0.25	0.25	1	1	0.5	0.5	0.5	0.5	0.5	0.5
CSP c	0.75	0.75	1	1	0.75	0.75	1	1	0.125	0.125	0.25	0.25	0.25	0.25	0.25	0.25
CSP d	1	1	1	1	1	1	0.25	0.25	1	1	0.25	0.25	0.25	0.25	0.25	0.25
CSP e	0.25	0.25	0.25	0.25	0.25	0.25	0.125	0.125	0.25	0.25	1	1	1	1	1	1

Table 2. CSP weighting factors. Clinical results at first visit (I) and follow-up visit (II): technical aspects (integrity, occlusal contacts, proximal contacts), patient satisfaction (Ps), handling, and biological aspects (plaque index (PI), gingival index (GI), bleeding on probing (BOP)). CSP a: unweighted, CSP b: dentist weighting, CSP c: patients weighting, CSP d: technical weighting, CSP e: biological weighting.

e-ISSN: 2320-7949
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DISCUSSION

Clinical Relevance

CSP is created as an instrument that is based on underlying technical, biological, and quality of life properties (subscores) and focuses on the application of an innovative procedure to measure the outcome in dental clinical trials. CSP was applied on a clinical trial on orally placed temporary restorations which are generally made of composite or methacrylate materials. The requirements for temporary restorations are essentially the same as those for definitive restorations [25]. Therefore, the CSP is designed not only to assess temporary restorations but also to assess fixed restorations with only minor modifications. Considering the large number of requirements for temporary restorations, it becomes clear that single primary parameters such as fracture of restoration or loss of retention only form a small proportion thereof. Thus, the significance of single primary parameters is limited with regard to the clinical rating of new treatment procedures or new materials. This applies in particular to forms of restorations with high success rates. For methodological reasons, the primary outcome measure of clinical trials has to be defined prior to the trial's start. Primary outcome measures such as survival, tooth loss, etc. has widely been chosen in many trials. However, dental clinical trials generally show good or excellent results if they only focus on primary outcome measures as mentioned above. Nevertheless, the approach is suffering of shortcomings regarding secondary outcome measures, as interactions between the different secondary outcome measures are disregarded. If, for example, data on the marginal gaps of implant restorations is collected and implant survival over time is recorded, the result could be full technical success due to good marginal integrity and implant survival. Still, the patients' perspective as well as functional or esthetical aspects remains unconsidered [26]. Thus, focussing on only one individual finding conceals the risk of other positive or negative effects remaining unnoticed. While the measurements of the probing depth can be used as a surrogate parameter for both periodontal health and the risk of tooth loss due to periodontal disease [8,12-15] there is no clinical parameter illustrating the changes concerning clinical success itself.

Therefore, the CSP has been developed in order to show the complete spectrum of clinical changes. Integrating weighting factors enables the CSP a dental, technical, subjective (dentist or patient) and biological rating of the treatment outcome. When the CSP was focused on patient satisfaction (CSP c), it showed a good evaluation value of the temporary restorations in terms of the mean value. This is also true for the CSP focused on biological parameters (CSP e) as the patients participating in the chosen clinical trial underwent a strict oral hygiene program as well as periodontal pre-treatment while they were also given information and instructions on the best individual oral hygiene measures while wearing the provisional restorations. On the other hand, CSP which is focused on dentist requirements (CSP b) as well as CSP which is focused on the technical aspects of temporary restorations (CSP d) were both able to reveal a minor decrease in terms of the mean value because a poor rating determined the overall rating.

The area-by-area comparison of the periodontal findings (plaque index, gingival index, bleeding on probing) using the mesial adjacent tooth as reference permits the differentiation between a general decrease in oral hygiene and periodontal disease induced by the temporary restoration itself. By comparing measurements with an adjacent tooth, not absolute values but differences are analysed. Thus, the individually measured value is less dominant within the whole range of measurements and the assessment principle, due to which the poorest rating determines the overall rating, leads to a risk-orientated CSP.

CONCLUSION

For clinical performance evaluation such as dental, technical, subjective (dentist or patient) and biological properties, the CSP rating system of the treatment outcome seems well suited for showing differences which would otherwise pass unnoticed. The integration of weighting factors allowed the differentiation between a large number of clinical parameters. Also, CSP can be focused and adapted for a wide range of specific outcome measures. Future efforts may be best focused on applying CSP as a cost-efficient method in dental clinical trials to achieve a large number of trials that can be compared easily.

REFERENCES

1. Cochrane NJ, et al. Remineralization models. Adv Dent Res. 2012;24:129-132.
2. Pak JG, et al. Prevalence of periapical radiolucency and root canal treatment: a systematic review of cross-sectional studies. J Endod. 2012;38:1170-1176.
3. Weijden VFA, et al. Safety of oscillating-rotating powered brushes compared to manual toothbrushes: A systematic review. J Periodontol. 2011;82:5-24.
4. Lee DW. Validated surrogate endpoints needed for peri-implantitis. Evid Based Dent. 2011;12:7.
5. Chadwick RG, et al. Development of a novel system for assessing tooth and restoration wear. J Dent. 1997;25:41.
6. Hujoel PP, et al. The effects of simple interventions on tooth mortality: Findings in one trial and implications for future studies. J Dent Res. 1997;76:867-874.

e-ISSN: 2320-7949
p-ISSN: 2322-0090

7. Steenberghe VD. Outcomes and their measurement in clinical trials of endosseous oral implants. Ann Periodontol. 1997;2:291-298.

8. Machtei EE. Outcome variables for the study of periodontal regeneration. Ann Periodontol. 1997;2:229-239.

9. National Institute of Health: Diagnosis and management of dental caries throughout life. NIH Consens Statement. 2001;18:1-23.

10. Castelnuovo J and Tjan AH. Temperature rise in pulpal chamber during fabrication of provisional resinous crowns. J Prosthet Dent. 1997;78:441-446.

11. Holloway RG and Dick AW. Clinical trial end points: on the road to nowhere? Neurology. 2002;58: 679-686.

12. Beck JD, et al. A 5-year study of attachment loss and tooth loss in community-dwelling older adults. J Periodontal Res. 1997;32:516-523.

13. Hujoel PP and DeRouen TA. A survey of endpoint characteristics in periodontal clinical trials published 1988-1992 and implications for future studies. J Clin Periodontol. 1995;22:397-407.

14. Hujoel PP, et al. Evaluating the validity of probing attachment loss as a surrogate for tooth mortality in a clinical trial on the elderly. J Dent Res. 1997;76:858-866.

15. Mandel ID. Overview of clinical trials of periodontal diagnosis methods and devices. Ann Periodontol. 1997;2:98-107.

16. Hernandez EP, et al. Mechanical properties of four methylmethacrylate-based resins for provisional fixed restorations. Biomed Mater Eng. 2004;14:107-122.

17. Ireland MF, et al. In vitro mechanical property comparison of four resins used for fabrication of provisional fixed restorations. J Prosthet Dent. 1998;80:158-162.

18. Medical Research Council: Guidelines for Good Clinical Practice in Clinical Trials. Aldrige Print Group, Mitcham, Surrey, UK; 1998.

19. World Medical Organization. Declaration of Helsinki. British Medical Journal 1996;313:1448-1449.

20. Silness J and Loe H. Periodontal disease in pregnancy II. Correlation between oral hygiene and periodontal condition. Acta Odontologica Scandinavica. 1964;22:21-35.

21. Loe H and Silness J. Periodontal disease in pregnancy I. Prevalence and severity. Acta Odontol Scand. 1963;21:533-551.

22. Luthardt RG, et al. Clinical study of the quality and processing of temporary crown and bridge acrylics. Article in German. Dtsch Zahnarztl Z. 1998;53:633-638.

23. Luthardt RG, et al. Clinical performance and periodontal outcome of temporary crowns and fixed partial dentures: A randomized clinical trial. J Prosthet Dent. 2000;83:32-39.

24. Ryge G. Clinical criteria. Int Dent J. 1980;30:347-358.

25. Gegauff AG. Provisional restorations. In: Rosenstiel SF, Land MF, Fujimoto J, editors. Conprovisional fixed prosthodontics. 2nd ed. St Louis: Mosby; 1995;325-360.

26. Roos J, et al. A qualitative and quantitative method for evaluating implant success: A 5 year retrospective analysis of the Brånemark implant. Int J Oral Maxillofac Implants. 1997;12:504-514.