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Guidance Means Accuracy: A Randomized Clinical Trial on Freehand vs. Guided Dental Implantation

Running title: An RCT on the Accuracy of Freehand vs. Guided Implantation

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Conflicts of interest: Endre Varga is the CEO of dicomLAB Dental, Ltd.; Gábor Braunitzer is the chief researcher of dicomLAB Dental, Ltd.

Author Contributions

E.V. contributed to conception, design and interpretation, drafted and critically revised the manuscript. M.A. contributed to conception, design and interpretation, drafted and critically revised the manuscript., L. M. contributed to conception and interpretation, acquisition, drafted and critically revised the manuscript., R. K. contributed to design, drafted and critically revised the manuscript., G. B. contributed to conception, design and interpretation, drafted and critically

revised the manuscript., J. P. contributed to conception, design and interpretation, drafted and critically revised the manuscript, and professionally supervised the research. All authors gave final approval and agree to be accountable for all aspects of the work.

Abstract

Objectives: A randomized clinical trial was conducted to compare all three known static guided surgery protocols (pilot, partial, full) with each other and with freehand surgery in terms of accuracy, under the same conditions.

Material and Methods: 207 implants of the same brand and type were placed in 101 partially edentulous volunteers in need of implantation in the mandible or maxilla or both. All cases were digitally planned, and the comparison of the planned and actual implant positions was performed using a medical image analysis software with dedicated algorithms. The primary outcome variable was angular deviation (AD, degrees). The secondary outcome variables were coronal global deviation (CGD, mm), apical global deviation (AGD, mm) and voxel overlap (VO, %).

Results: AD showed stepwise improvement in significant steps as the amount of guidance increased. The highest mean AD ($7.03^{\circ} \pm 3.44$) was obtained by freehand surgery, and the lowest by fully guided surgery ($3.04^{\circ} \pm 1.51$). As for the secondary outcome variables, all guided protocols turned out to be significantly superior to freehand surgery, but they were not always significantly different from each other.

Conclusions: As for the comparison that this study sought to perform, it can be said that the static guided approach significantly improves the accuracy of dental implant surgery as compared to freehand surgery. Furthermore, the results suggest that any degree of guidance yields better results than freehand surgery and that increasing the level of guidance increases accuracy.

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Introduction

Today's commercially available dental implants are characterized by fairly good survival and clinical success rates, even in risk populations (De Angelis et al., 2017; Derks et al., 2015; van Velzen et al., 2015), thus the main focus of investigation has shifted from osseointegration toward the three-dimensional positioning of implants. There are two main reasons for this. First, correct positioning is considered a prerequisite for an optimal esthetic outcome (Tahmaseb et al., 2014). Second, implant malpositioning increases the risk of complications. Canullo and colleagues estimated that nearly half of the peri-implantitis cases could be traced back to implant malpositioning (Canullo et al., 2016).

Surgical guides aim to reduce the inherent positional uncertainty of freehand surgery. Such guides are classified into two main categories: dynamic and static.

Dynamic systems offer real-time visualization during surgery, but their accuracy is lower than that of static systems (Jung et al., 2009). Furthermore, they are expensive, occupy considerable space (Younes et al., 2018), and their use is not always straightforward (Jorba-Garcia et al., 2019).

Static systems are template-based, and their accuracy is acceptable in most clinical situations (Tahmaseb et al., 2018). Such templates are mostly fabricated via 3D printing based on digital images (CBCT/intraoral scanner), and the resulting template is either bone-, mucosa-, or tooth-supported (Behneke et al., 2012; Ersoy et al., 2008; Nickenig et al., 2010; Ozan et al., 2011). Kühl et al. (2015) concluded that a high accuracy can be achieved using printed templates, and the same group also reported that a higher accuracy of implant placement can be achieved by using three-dimensional printed templates produced by matching a surface scan and CBCT as compared with

templates which use physical elements transferring the virtual planning into reality (Kernen et al., 2016). Finally, systematic reviews suggest that tooth-supported templates yield the highest accuracy (Marliere et al., 2018; Tahmaseb et al., 2014; Van Assche et al., 2012).

The templates are used according to three different protocols, defined by the degree of guidance. The pilot protocol uses the template only for the initial drill (“pilot drill”), and the resulting bony socket is supposed to guide subsequent osteotomies and implant placement. The partially (or half-) guided protocol uses the template for all osteotomies, only implant placement is performed without the template. Partial guidance is a kind of universal solution, which provides the maximum guidance achievable with any implant system that does not have a fully guided kit. Finally, the fully guided protocol uses the template from the first drilling through implant placement. Regardless of protocol, all drills are used at full length (controlled with a stop). The sequence of osteotomies determines only the final diameter of the resulting socket.

Most studies have focused on the accuracy of the full protocol, and their results indicate that full guidance yields higher accuracy than lower levels of guidance (Tahmaseb et al., 2014; Tahmaseb et al., 2018; Van Assche et al., 2012), though the difference is not always significant (Kuhl et al., 2013). Less attention has been paid to the pilot and partial protocols and freehand surgery (Di Giacomo et al., 2005; Vercruyssen et al., 2014; Vercruyssen et al., 2015; Younes et al., 2019), even though the former are widespread, and the latter is still considered to be the standard by many. The accuracy of tooth-supported guides for partial edentulous cases (Arisan et al., 2010) is another under-discussed aspect, while it is safe to assume that partial edentulousness is a frequent reason for dental implantation. Finally, remarkably few RCTs are available on template-based dental implant surgery in general (Vercruyssen et al., 2014; Younes et al., 2018).

To our knowledge, no prior RCT has compared all three static guided protocols with each other and with freehand surgery in terms of accuracy and under homogenous conditions. Therefore, the objective of this study was to perform that comparison in a larger sample of partially edentulous volunteers, using a stereolithographically fabricated, tooth-supported surgical guide. We hypothesized that the guided protocols would yield a significantly higher level of accuracy than freehand surgery. For the purposes of this study, accuracy is defined as the closeness of spatial agreement between any given implant as planned (reference) and as inserted (measurement), expressed by four spatial deviation parameters.

Material and Methods

Participants

In July 2018, all major public service institutions of the city of Szeged, Hungary were sent an e-mail request to let the employees know that volunteers were being recruited for a dental implantation study. Those who responded to this call were screened at the Department of Oral and Maxillofacial Surgery, Faculty of Medicine, University of Szeged, Hungary, where later all interventions and data collection took place. The inclusion criteria were:

- Age between 18 and 75 years
- Either sex (see restriction under exclusion criteria)
- Partial edentulousness in the mandible or maxilla (1 to 6 teeth, maximum 3 in a row)
- Clinical situation fit for implantation as judged by the examining physician or principal investigator (satisfactory soft and hard tissue conditions and occlusion)
- Good communication with the examiner and expected compliance
- Signed informed consent

The exclusion criteria were:

- Pregnancy or lactation
- Female sex, childbearing age, no contraception (for reasons of radiation safety)
- Conditions that might render intraoral manipulation impossible (limited mouth opening, excessive gag reflex)
- Bisphosphonate treatment (either at the time of screening or in the history)
- Radiotherapy, irradiation of the mandible or the maxilla (either at the time of screening or in the history)
- INR > 2.5
- Known HIV, Hepatitis B or Hepatitis C infection
- Known allergy to any component of the implant or the implant guide
- Poor oral hygiene
- Substance abuse
- Smoking
- Untreated periodontal disease

- Any disease or condition that, in the opinion of the principal investigator, would risk participation until the end of the study / because of which the volunteer would be put at unacceptable risk by participation

The study conformed to the Helsinki Declaration of 1975 as revised in 2000 and the principles of Good Clinical Practice. The protocol was approved by the National Institute of Pharmacy and Nutrition of Hungary (Approval No. OGYÉI/29862/2018). The study is registered on clinicaltrials.gov (ID: NCT03854162), and the full protocol is available from the corresponding author.

Trial Design

The trial followed a parallel design, with volunteers randomly assigned to one of the following study arms: freehand surgery (Fr), pilot guide protocol (Pi), partial guide protocol (Pa) or fully guided surgery (Fu).

The Surgical Guide Manufacturing System

SMART Guide is an ISO 1348 certified comprehensive digital surgical planning and template manufacturing system for dental implantological purposes, developed and provided by dicomLAB Dental (Szeged, Hungary; henceforth: service provider). SMART Guide uses a standardized workflow, in which information and materials/products are transferred between three sites: the dentist's office, an imaging lab, and dicomLAB's production hub. The workflow is designed in a way that the dentist has to perform only tasks that require dental professional competence. IT tasks, such as the registration of images (i.e. the superimposition of the diagnostic image of the patient and the image of the impression), preparation for 3D printing, and 3D printing itself are performed by specially trained dental technicians in the production hub. The input of the workflow is imaging information (CBCT images), and the output is a custom-made surgical guide with a surgical protocol that tells the end user how to use the chosen surgical kit in the given case. The workflow is summarized in Figure 1.

First, the dentist takes a silicone impression of the patient's dentition. Then the patient brings the impression to the imaging laboratory (this is not necessarily separate from the dentist's office) where two CBCT images are taken: one of the impression and one of the patient. The resulting

images are uploaded to the server of the production hub. The dental technicians of the production hub prepare the case for planning in a dedicated software. The resulting 3D virtual model of the patient's anatomy is then downloaded by the dentist, who plans the surgery in a planning software provided by dicomLAB as part of the system (Figure 2). By ordering the plan, the dentist uploads it to the production hub once again so that the technicians can produce the surgical guide and the corresponding surgical protocol. The protocol is individually generated for each case by the software which is used for turning the dentist's plan into a printable form. The protocol tells the dentist how to use the surgical instruments in the given case to get the planned results (Figure 3). The surgical guide and protocol are delivered to the dentist's office. The surgical guide may be used immediately after disinfection in cold sterilization solution.

Virtual Implant Planning

Cone beam computer tomographies were acquired (iCAT Next Generation, iCAT, USA) with standard settings for all patients (120 kV, 5mA, 9 sec, voxel size: 250 μ m, FOV: 110 mm; all scans in this study were done with these specifications). A bite block was used to ensure non-occlusion and a correct head position. A silicone impression (Zetaplus[®], Zhermack, Italy) was taken in a plastic tray (hi-tray, Zhermack, Italy), and it was scanned separately.

The two scans were sent online to the service provider, where they were registered, and a ready-to-plan case was sent back to the surgeon. The surgeons then planned the surgeries with their own copy of the planning software (SMART Guide, dicomLAB, Hungary) and sent the plan back for production. The surgeons always planned their own cases. The surgical templates were 3D printed with a multijet technology printer (ProJet MD3510, 3D Systems, USA). To each template, a case-specific protocol was enclosed, with directions to the surgeon about the use of tools during the surgery. For the freehand cases, no template was produced, but the plans and protocols (henceforth: the plan) were sent back to the surgeons for use with the surgeries. For the guided cases, surgeons were provided with the proper toolkits and surgical templates as well.

Presurgical Procedures

All volunteers underwent ultrasonic scaling 7 \pm 2 days before the planned date of surgery. Volunteers were educated regarding the importance of maintaining good oral hygiene and

individualized advice was offered. The local prophylactic protocol was followed (amoxicillin/clavulanic acid 2000 mg per os or clindamycin 600 mg per os 60 minutes prior to surgery). After administration of local anesthetics, volunteers were instructed to rinse with 0.2% chlorhexidine solution for 30 seconds (Corsodyl[®], GlaxoSmithKline, UK). The volunteers then underwent the surgery. All surgeries were performed by the same two experienced surgeons, who had been trained and calibrated before the actual surgeries began to assure performance at the same level.

Surgical Procedures

Freehand surgery: A midcrestal incision was made at the implant recipient site, sulcular incisions were made on the mesial aspects of the adjacent teeth, and a full-thickness flap was elevated. The surgeons had the plan at their disposal for orientation throughout the surgery, but they had no physical guidance at all. In other words, they relied entirely on mental navigation. Implants were inserted as per the manufacturer's instructions, then a cover screw was placed, and the flap was closed. Non-absorbable silk monofilament sutures (Silkam[®], Braun, Germany) were used for all surgeries. A postoperative CBCT scan was done 2 ± 1 days following the surgery, the sutures were removed 7 ± 1 days following the surgery, and the final follow-up visit was due 14 ± 2 weeks later. Access preparation, implant insertion, wound closure and postoperative recalls were the same for all protocols.

Pilot Guide Protocol: After access preparation, the template was placed, and the first osteotomy was performed through it, with a 2.0 mm diameter pilot drill (dicomLAB Dental, Hungary). The resulting bony socket served to guide the rest of the osteotomies. The surgeons had the plan at their disposal for orientation throughout the surgery, but after the first osteotomy, they had no physical guidance.

Partial Guide Protocol: After access preparation, the template was placed, and all osteotomies were performed through it. The only non-guided step was implant insertion. For the osteotomies, the universal surgical kit of SMART Guide was used. The surgeons had the plan at their disposal for orientation throughout the surgery, and the template provided physical guidance up to the final osteotomy. For these cases, the surgeons also used the surgical protocol (see Figure 3).

Fully Guided Surgery: After access preparation, the template was placed, and both the osteotomies and implant insertion were performed through it. The guided surgical kits of Alpha-Bio Tec

(Israel) were used. The surgeons had the plan at their disposal for orientation, and the guide provided physical guidance up to the insertion of the implant. For these cases, the surgeons also used the surgical protocol (see Figure 3).

All implants were MultiNeO[®] of various dimensions (Alpha-Bio Tec, Israel).

The prosthetic management of the studied population is part of another protocol and thus is not reported here.

Sample Size

The required sample size was calculated in SAS 9.4 (SAS, USA) for the primary outcome variable (AD). Sample size calculation was performed to obtain a sufficient number of samples for pairwise t-tests. 6 pairwise tests were planned (all possible pairs of treatment groups), thus alpha was set to 0.008 to have an overall significance level not larger than 5% ($p \leq 0.05$). The target power was set to 80%.

Preliminary data from the literature was available for Fu ($3.53 \pm 2.05^\circ$), Pa ($5.13 \pm 2.05^\circ$) and Fr ($10.64 \pm 5.52^\circ$). These values were calculated from the data published in the systematic reviews of Tahmaseb et al. (2014) and Bover-Ramos et al. (2017). The required sample sizes were calculated separately for the Fu-Pa and the Fu-Fr comparisons. As for the Fu-Pa comparison, based on our experience, we expected a somewhat larger difference, so we calculated with a difference of 2° , instead of 1.62° as indicated by data from the literature. As no reliable data for Pi were available, no a priori calculations were performed for this variable. To correct for the design effect, IRR was set to 0.2 and 2 samples (implants) per volunteer were assumed. This way, the required number of implants turned out to be $n=47$ for the Fu-Pa comparison and $n=22$ for the Fr-Pa comparison. Thus, the target sample size was 47 samples per study arm.

An interim analysis was planned when reaching the target sample size. In this interim analysis no comparisons would be made, only the actual mean differences, standard deviations, and IRR would be calculated to have actual data for sample size re-calculation.

Randomization

Randomization was done in nQuery Advisor 6.01 (StatSols, Ireland) by AdWare, Ltd. Two consecutive randomizations were performed, both for $N=120$, a block size of 4 and an allocation ratio of 1:1:1:1 by AdWare, Ltd. First, 120 ordinal numbers (30 of each study arm, each number

representing a future volunteer) were randomly assigned to the two surgeons, represented by the letters A and B. This added up to the first part of the volunteer code, like A001 or B032. Second, the code fragments generated in the first step were randomly assigned to the four arms of the study, which resulted in the second part of the code, similarly a four-digit unit, always starting with R (like R003). This was done for the cases of each surgeon separately. The numbering for the cases of surgeon A started from 001, while for those of surgeon B from 101. The numbers were assigned to study arms in quads, so that the first number always meant “freehand”, the second “pilot”, the third “partial” and the fourth “full”. Once this was ready, the volunteers were randomly assigned to study arms. This was the second randomization. The entire procedure resulted in a six-digit code in the format A001-R001 and determined both the treating surgeon and the study arm. The codes were then put in closed envelopes marked with the enrollment number (a simple ordinal number to indicate the number of any given volunteer in the enrollment order, so #1 stood for the first enrolled volunteer, #2 for the second, etc.). The envelopes were opened at the time of enrollment, the code was deciphered by the on-site monitor with the help of a key provided by AdWare, Ltd., and it was entered into the volunteer’s documentation immediately.

Data Analyses

Accuracy analyses were conducted in Amira 5.4.0 (Thermo Fisher Scientific, USA) with dedicated algorithms. Pre- and postoperative CBCT scans of any given patient were registered. For this registration, the region of interest was confined to the analyzed area to avoid inaccuracy due to different pre/post mouth opening. The inserted implants were then manually segmented and transformed into a three-dimensional model. The corresponding implantation plan was extracted from the database of dicomLAB and applied to a model corresponding to the inserted implant in its dimensions. This model was duplicated, and the duplicate was aligned with the segmented model. Finally, the model implant in the planned position was compared to the model implant in the aligned position. The main steps of the analysis are shown in Figure 4, and the outcome variables are explained in Figure 5.

The expert who performed the digital comparisons was blinded to the aim of the study and could identify datasets only by codes, which rendered it impossible for him to decipher the group membership of any given dataset.

Analyses for randomly chosen 25 implants were carried out in triplicate to allow calculation of intraclass correlation coefficients. This calculation was used to express the reliability of our measurement method (algorithms). The intraclass correlation coefficient is a fraction that expresses the degree of agreement between consecutive measurements. The higher the value of this fraction is, the greater the agreement, and the more reliable the method. Values over 0.9 are considered to express excellent agreement, and, in this specific case, imply that the method is highly reliable.

Outcomes

The primary outcome was angular deviation (AD) defined as the angle closed by the principal axis of the planned implant and the principal axis of the inserted implant in degrees. The secondary outcomes were: coronal global deviation (CGD; the distance between the center of the coronal end of the planned and the inserted implants in millimeters), apical global deviation (AGD; the distance between the apical endpoints of the planned and the inserted implants in millimeters), and voxel overlap (VO; the overlap between the voxels of the planned and the inserted implants in percent). The latter was introduced as a proxy measure of global accuracy. See also Figure 5.

Statistical Analyses

Demographic data were analyzed descriptively. Categorical variables were described with the number of observations and relative percentages. Continuous variables were described with the number of cases, mean, standard deviation, median, minimum and maximum. Besides the pairwise t-tests, mixed-model ANOVA was used to compare the target variables across the four arms of the study. Treatment and surgeon were used as fixed effects and patient as random effect. The Tukey-Kramer method was applied for the adjustment of confidence intervals and p-values. As the sample size estimation was originally performed assuming t-tests, 95% confidence intervals were calculated for the least-squares means of the pairwise differences in order to show the robustness of the results. To check the possible clustering effect of the implants within the same patients, intraclass correlation coefficient of the outcome within the patients was calculated for each target variable. Intraclass correlation coefficients were also used to express the reliability of the method of measurement (see above). Statistical analyses were conducted in SAS 9.4 (SAS, USA).

To avoid bias, all data management was outsourced to independent companies (see Acknowledgements). Their reports are available upon request.

Results

Recruitment of volunteers took place from 5/7/2018 through 9/1/2018. The surgeries took place between 9/14/2018 and 11/11/2018. Follow-up ended on 2/28/2019. The flow of participants is shown in Figure 6.

Data from the per-protocol population (n=101) were analyzed. The characterization of the per-protocol population is given in Table 1.

Two hundred and seven implants were placed. Of these implants, 137 were placed in mandibulae and 70 in maxillae. The implants were distributed roughly equally in the four quadrants across all four study arms, with the clear predominance of the posterior region (97.5% of all placed implants). Single gaps were treated the most frequently (147 implants altogether), followed by double gaps (59 implants), and in a single case, 3 missing roots were replaced in a row. Table 2 summarizes these relations by study arm. The dimensions of the placed implants were as follows (diameter/length (N)): 3.2/10 (2), 3.2/11.5 (2), 3.5/10 (12), 3.5/11.5 (13), 3.5/13(8), 3.75/10 (25), 3.75/11.5 (42), 3.75/13 (11), 4.2/10 (55), 4.2/11.5 (19), 4.2/13 (7), 4.2/8 (4), 5/11.5 (3), 5/8 (4).

The sample size was re-calculated with the available study data and corrected by the actual design effect calculated using the actual IRR value. The average number of samples per patient was 2.07, the intraclass correlation coefficient was 0.1770 and thus the design effect was $Deff=1+0.177*(2.07-1)=1.189$.

The sample size re-calculation showed that the number of implants was sufficient for the Fr-Fu and Fr-Pa comparisons, as well as for the Fu-Pa comparisons. However, to ensure at least 80% power for the remaining 3 comparisons, more than 100 implants per study arm would have been required. We weighed this cost against the benefits of having 80% statistical power for those comparisons and decided that it would be ethically unacceptable to recruit more volunteers only for statistical power. Thus, the study was terminated at this point. Comparisons were performed as planned but we call the reader's attention that the results of the remaining comparisons (Fr-Pi, Pi-Pa, Pi-Fu) are to be interpreted only in a descriptive manner.

No harm or unintended effects were registered.

Outcomes

The mixed model showed no significant difference between the surgeons ($p= 0.6880$), but indicated highly significant differences between the study arms ($p< 0.0001$)

AD: the largest mean AD was measured in Fr (7.03°), and AD gradually decreased with increasing guidance, so that the smallest mean AD was measured in Fu (3.04°). The t-tests indicated significant difference for Fr-Pa, Fr-Fu, and Pi-Fu. Standard deviations were similar in Fr, Pi, and Pa, while Fu showed considerably smaller SD. The mixed model ANOVA indicated significant difference in the same comparisons (see Table 4 for the Tukey-Kramer results).

CGD: CGDs and corresponding SDs gradually decreased with increasing guidance. Mean CGD was the highest in Fr (1.82 mm), and the lowest in Fu (1.40 mm). Neither the t-tests nor the mixed model ANOVA indicated significant differences (see Table 4 for the Tukey-Kramer results).

AGD: AGDs and corresponding SDs gradually decreased with increasing guidance. The t-tests indicated significant difference for Fr-Pi, Fr-Pa, and Fr-Fu. Mean AGD was the highest in Fr (2.43 mm), and the lowest in Fu (1.59 mm). The results of the mixed model ANOVA were in agreement with those of the t-tests (see Table 4 for the Tukey-Kramer results).

VO: the largest mean VO was measured in Pa (60.26%), and the smallest in Fr (39.98%). The t-tests indicated significant difference for Fr-Pi, Fr-Pa, and Fr-Fu. The highest SD was observed in Fr and the lowest in Pa. The results of the mixed model ANOVA supported the results of the t-tests (see Table 4 for the Tukey-Kramer results).

Hypothesis tests by mandible/maxilla were not conducted because of the small size of the resulting subsamples. Descriptive statistics, however, are given in Table 3. Given the similarity of the results from the two bones and the small number of maxillary observations, it is safe to assume that merging the two datasets for the hypothesis tests did not skew the results.

The within-patients intraclass correlation coefficients were 0.1770 (AD), 0.4924 (CGD), 0.4317 (AGD) and 0.4323 (VO).

The intraclass correlation coefficients calculated to characterize the method of measurement indicated excellent reliability for all four variables: 0.973 (AD), 0.957 (CGD), 0.963 (AGD) and 0.998 (VO).

For detailed results, see Table 3, Table 4 and Figure 7.

Discussion

To our knowledge, this is the first RCT to compare all three known types of static guided dental implant surgery with each other and with freehand surgery in terms of accuracy in a large sample. The results are in accordance with the literature (Arisan et al., 2010; Di Giacomo et al., 2005; Nickenig et al., 2010; Tahmaseb et al., 2018; Vercruyssen et al., 2014; Younes et al., 2018) and suggest that the higher the level of guidance is, the higher the correspondence will be between the planned and the actual implant position. This is especially well illustrated by the primary outcome (AD), which improved in significant steps corresponding to increasing guidance, with standard deviations decreasing in parallel. To put it simply: freehand surgery yielded the poorest, and fully guided surgery the best results. We found a mean AD of 7.03° for Fr. Similar clinical studies conducted with static guides and in partial edentulousness reported 6.99° (Younes et al., 2018), and 9.8° (Nickenig et al., 2010). In our study, Pi yielded a mean AD of 5.71° , comparable to the 5.95° reported in the study of Younes et al. (2018). As for Pa, Di Giacomo et al. (2005) reported 7.25° and Nickenig et al. (2010) 4.2° . Our finding in this study was a mean of 4.3° . Finally, Fu in this study yielded a mean error of 3.04° . Of the comparable studies, Younes et al. (2018) reported 2.3° , and Arisan et al. (2010) 3.39° .

Accurate angulation is important not only for esthetic and biomechanical reasons but also because misangulation can interfere with the prosthetic plan. Considerable deviation from the planned angulation might necessitate an angulated abutment, or, if screw-retained restoration was planned, cemented restoration might have to be used instead. Screw-retained restorations, which have several advantages over cemented ones and are getting widespread for that reason (Assaf and Abu Gharbyeh, 2014), are particularly sensitive to angulation issues (Bidra, 2016; Gjelvold et al., 2016).

As for the secondary outcome variables, which we do not discuss in detail for reasons of space, the results showed a characteristic pattern: all guided protocols turned out to be significantly superior to freehand surgery, but they were not significantly different from each other. The exception is CGD, which did not show significant improvement with increasing guidance, but this is obviously due to the fact that the study was underpowered for the detection of significant differences in the tenth-millimeter range. Younes et al. (2018) reported similar findings (except for Pa, which they

did not examine). Unfortunately, the authors published their results as mean (SE), instead of mean (SD), which makes comparison difficult, even if their means are quite close to ours (see above).

It is important to point out that the results yielded by Pa were quite close to Fu regarding all parameters, which shows that a safe guided option is available when the accuracy of Pi is not enough, but the applied implant system does not offer a guided solution.

The new measure, voxel overlap, seems to correlate most closely with CGD and AGD, and it appears to be a valid single-number indicator of positional accuracy, but it must be admitted that the standard deviations are still quite high. The reason for this might be that the method is sensitive to the contrast threshold set at segmentation, which, in turn, determines the voxel content of the resulting model. This is an eliminable problem that needs to be addressed.

Finally, the following limitations must be noted: first, this study was properly powered for the detection of significant differences for the primary outcome variable in the Fr-Pa, Fr-Fu and Pa-Fu comparisons; second, in this study we used global measures, that is, for the coronal and apical deviations, we did not separate the vertical and horizontal components; third, the study allows only a descriptive interpretation of the difference between mandibular and maxillary surgeries; fourth, the results are generalizable only to partial edentulous situations when a static guide system is used.

Within the limitations of this study, we conclude that any degree of static guidance improves the accuracy of dental implant surgery as compared to freehand surgery in general, and it has the most pronounced and significant effect on angular deviation in particular. Considering the importance of accurate implant placement in terms of aesthetics, function and complication avoidance, our findings support the claim of Younes et al. (2018) that guided surgery “should be the gold standard approach instead of freehand surgery when perfect implant positioning is required.”

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Figure Legends

Figure 1. The surgical guide production workflow. The numbers indicate the consecutive steps of the process. Note that the planning surgeon already has the plan, that is why it is not delivered again after guide printing.

Figure 2. Surgical plan in the planning software in three views. In this particular case, the diameter of the planned implant was 3.75 mm, and its length was 10 mm. The surgical protocol shown in Figure 3 was generated on the basis of this plan. This plan the operators always had with them during the surgeries to help orientation, regardless of study arm.

Figure 3. A surgical protocol of the SMART Guide system (full guide, see plan in Figure 2). The protocol defines the sequence in which the instruments of the selected surgical kit must be used in the given case (Alpha-Bio Tec's guided surgery kit in this case). Note that three possible sequences are recommended, depending on the hardness of the bone. This protocol the operators only had with them for the partially and fully guided surgeries (in a freehand or pilot case, such a protocol does not have any meaning).

Figure 4. Main steps of the analysis. 1: The preoperative (a) and postoperative (b) scans as three-dimensional models. It is readily observable that without further adjustment, the two models are not in the same spatial position, which necessitates adjustment; 2: Differences in the degree of jaw opening between the pre- and postoperative scans might interfere with the accuracy of registration, so the analysis concentrates only on the target area: in this case, only the maxilla is used, the rest of the model is eliminated; 3: The pre- and postoperative scans are merged to allow implant segmentation; 4: The basis of the segmentation is the homogeneous radiopacity of the implant. Here the segmented implant (red) is shown in the segmentation editor, in three different views; 5: Based on the segmentation, a three-dimensional model is generated (blue), and another implant

model (of the same dimensions as the one actually inserted, red) is added in the planned position.
6. The bone model is removed for better visibility and the comparator algorithm is applied.

Figure 5. Comparison of the planned (red) and actual (blue) implant positions, demonstrated on two model implants (maxillary position). AD: angular deviation; CGD: coronal global deviation; AGD: apical global deviation; VO: voxel overlap. $A_{1,2}$: axes of the two models; $a_{1,2}$: apical midpoints; $c_{1,2}$: coronal midpoints. An apical or coronal midpoint is where the axis of the given model crosses the apical or coronal surface, respectively.

Figure 6. CONSORT flowchart

Figure 7. Box-plots presenting AD(A), CGD(B), AGD(C) and VO(D) for all 207 placed implants, by study arm. Bottom whisker: minimum value, box bottom: Q1 (25th percentile), line: median, box top: Q3 (75th percentile), top whisker: maximum value, dots: outliers.

Arm	Sex	N	%	Mean age (yr)	SD	Min.	Median	Max.	Bone	N	%
Fr (N=26)	M	13	50.00	40.38	7.15	24	40	56	Mand.	37	67.3
	F	13	50.00						Max.	18	32.7
Pi (N=23)	M	8	34.78	41.96	7.49	29	41	57	Mand.	29	59.2
	F	15	65.22						Max.	20	40.8
Pa (N=24)	M	14	58.33	40.63	9.23	26	41.5	56	Mand.	34	66.7
	F	10	41.67						Max.	17	33.3
Fu (N=28)	M	15	53.57	42.11	8.23	23	43	56	Mand.	37	71.2
	F	13	46.43						Max.	15	28.8

Table 1. Demographic characteristics of the study population and the distribution of the placed implants between the mandible and the maxilla. Fr: freehand surgery; Pi: pilot guide protocol; Pa: partial guide protocol; Fu: fully guided surgery

Arm	Single	Double	Triple	End of Arch
Fr	39*	8**		5***
Pi	34	6		1
Pa	33	7	1**	3
Fu	41	9		5

Table 2. Distribution of single and double gaps across the arms of the study. *number of implants; **number of observations ($n_{\text{implants}}/2$); ***included in single, double and triple.

FULL SAMPLE											
AD (degrees)							CGD (mm)				
Treatment	N	Mean	SD	Min.	Median	Max.	Mean	SD	Min.	Median	Max.
Fr	55	7.03	3.44	0.71	6.40	21.3	1.82	0.94	0.56	1.56	5.38
Pi	49	5.71	3.68	1.00	4.70	17.0	1.57	0.91	0.27	1.35	4.06
Pa	51	4.30	3.33	0.52	3.30	15.9	1.37	0.79	0.31	1.29	3.48
Fu	52	3.04	1.51	0.42	2.65	6.30	1.40	0.54	0.49	1.36	2.94
AGD (mm)							VO (%)				
Treatment	N	Mean	SD	Min.	Median	Max.	Mean	SD	Min.	Median	Max.
Fr	55	2.43	0.98	0.54	2.27	4.83	40.57	22.34	0.00	42.06	88.13
Pi	49	1.86	1.09	0.44	1.59	5.05	55.83	24.50	0.00	62.65	87.04
Pa	51	1.59	0.86	0.28	1.44	4.24	60.37	20.64	1.92	62.87	93.64
Fu	52	1.59	0.59	0.31	1.53	2.99	58.82	15.63	12.08	64.09	84.38
MANDIBLE											
AD (degrees)							CGD (mm)				
Treatment	N	Mean	SD	Min.	Median	Max.	Mean	SD	Min.	Median	Max.
Fr	37	6.98	3.78	0.70	6.10	21.30	1.84	1.05	0.56	1.56	5.38
Pi	29	6.01	3.44	1.30	5.30	15.50	1.69	1.06	0.27	1.47	4.06
Pa	34	4.37	3.62	0.60	3.20	15.90	1.21	0.73	0.33	1.11	3.18
Fu	37	3.05	1.42	0.40	2.70	6.00	1.34	0.58	0.49	1.24	2.94
AGD (mm)							VO (%)				
Treatment	N	Mean	SD	Min.	Median	Max.	Mean	SD	Min.	Median	Max.
Fr	37	2.30	1.02	0.54	1.97	4.83	39.98	22.64	0.00	45.94	88.13
Pi	29	1.95	1.28	0.45	1.57	5.05	50.12	27.77	0.00	58.36	84.61
Pa	34	1.41	0.83	0.28	1.39	3.88	60.26	22.36	2.41	63.59	93.64
Fu	37	1.62	0.61	0.55	1.52	2.99	58.32	14.82	12.08	63.95	84.38
MAXILLA											
AD (degrees)							CGD (mm)				
Treatment	N	Mean	SD	Min.	Median	Max.	Mean	SD	Min.	Median	Max.
Fr	18	7.13	2.69	3.6	6.65	14.60	1.76	0.70	0.68	1.83	3.28
Pi	20	5.26	4.05	1.0	4.15	17.00	1.38	0.63	0.42	1.32	2.30
Pa	17	4.14	2.75	0.5	3.30	11.80	1.51	0.73	0.31	1.58	3.07
Fu	15	3.04	1.78	0.6	2.60	6.30	1.54	0.39	0.97	1.48	2.53
AGD (mm)							VO (%)				
Treatment	N	Mean	SD	Min.	Median	Max.	Mean	SD	Min.	Median	Max.
Fr	18	2.42	0.90	0.93	1.92	4.05	41.77	22.32	8.18	33.55	76.56
Pi	20	1.72	0.77	0.44	1.86	2.81	64.11	16.08	38.77	66.47	87.04
Pa	17	1.83	0.71	0.75	1.70	3.02	56.61	12.14	29.55	64.82	78.92
Fu	15	1.53	0.536	0.31	1.55	2.55	60.08	12.66	26.16	64.22	77.69

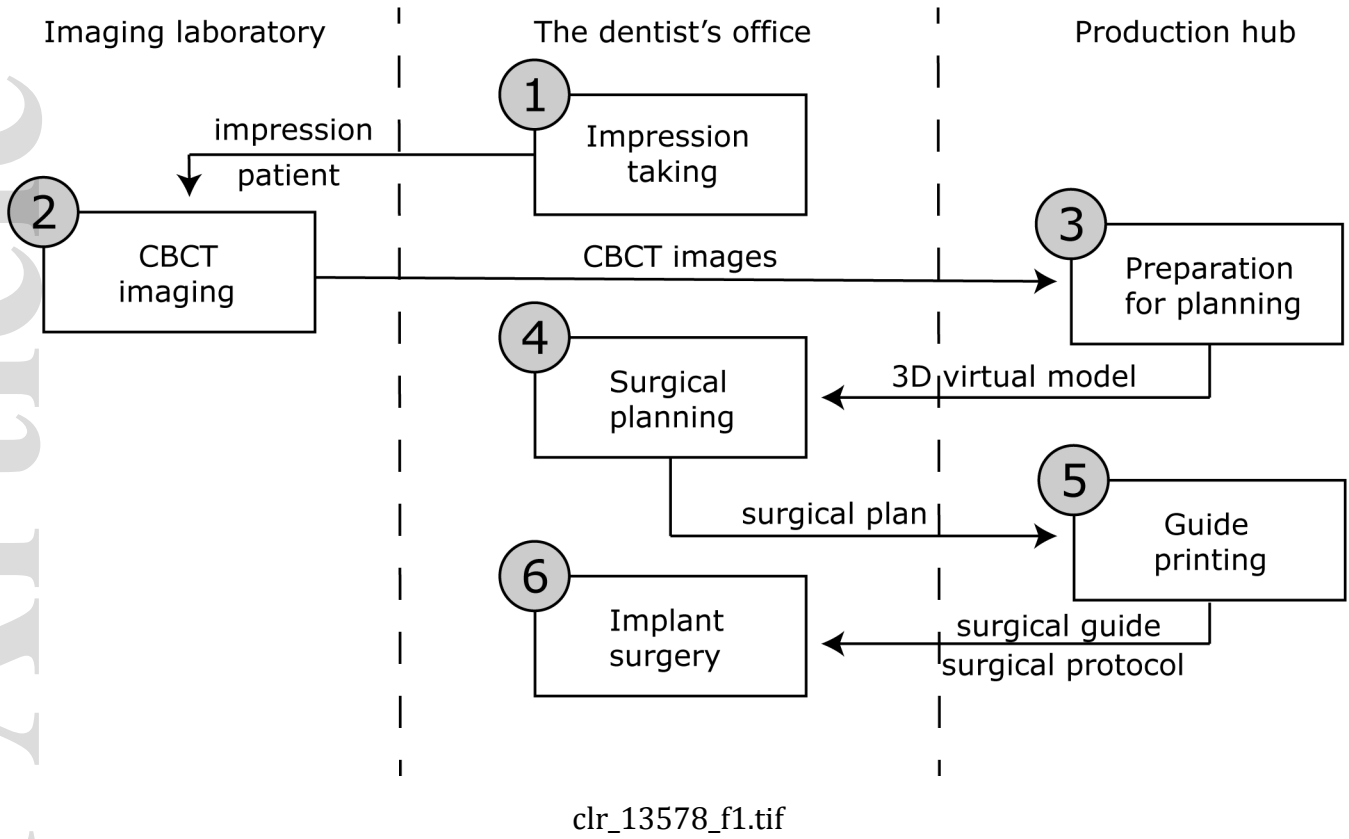
Table 3. Descriptive statistics of the outcomes.

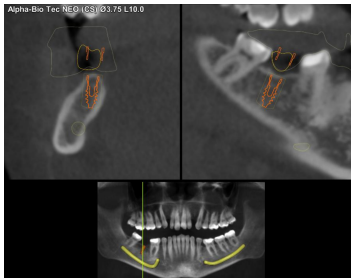
Comparison AD	Estimate	Adj.Lower	Adj.Upper	Adj.p	Effect size
Fr vs. Pi	1.2643	-0.3840	2.9126	0.1937	0.37092
Fr vs. Pa	2.7459	1.1180	4.3738	0.0001*	0.80553
Fr vs. Fu	3.9828	2.3631	5.6025	<.0001*	1.49965
Pi vs. Pa	1.4816	-0.1973	3.1606	0.1037	0.40018
Pi vs. Fu	2.7185	1.0515	4.3855	0.0003*	0.94590
Pa vs. Fu	1.2369	-0.4140	2.8878	0.2115	0.48665
Comparison CGD	Estimate	Adj.Lower	Adj.Upper	Adj.p	Effect size
Fr vs. Pi	0.2903	-0.2532	0.8337	0.5059	0.26747
Fr vs. Pa	0.5165	-0.01896	1.0519	0.0629	0.51725
Fr vs. Fu	0.3761	-0.1475	0.8997	0.2450	0.54079
Pi vs. Pa	0.2262	-0.3266	0.7791	0.7096	0.23555
Pi vs. Fu	0.08584	-0.4541	0.6257	0.9758	0.22184
Pa vs. Fu	-0.1404	-0.6733	0.3925	0.9016	0.05161
Comparison AGD	Estimate	Adj.Lower	Adj.Upper	Adj.p	Effect size
Fr vs. Pi	0.5136	-0.07024	1.0974	0.1054	0.46520
Fr vs. Pa	0.8457	0.2707	1.4206	0.0012*	0.81133
Fr vs. Fu	0.7304	0.1662	1.2946	0.0055*	0.92916
Pi vs. Pa	0.3321	-0.2618	0.9260	0.4654	0.27003
Pi vs. Fu	0.2169	-0.3650	0.7987	0.7651	0.30369
Pa vs. Fu	-0.1152	-0.6895	0.4590	0.9532	0.00035
Comparison VO	Estimate	Adj.Lower	Adj.Upper	Adj.p	Effect size
Fr vs. Pi	-15.1719	-28.6605	-1.6833	0.0209*	0.65099
Fr vs. Pa	-22.1234	-35.4071	-8.8397	0.0002*	0.92070
Fr vs. Fu	-18.0718	-31.1097	-5.0338	0.0025*	0.94686
Pi vs. Pa	-6.9515	-20.6726	6.7697	0.5508	0.20047
Pi vs. Fu	-2.8999	-16.3455	10.5458	0.9428	0.14572
Pa vs. Fu	4.0516	-9.2193	17.3226	0.8557	0.08447

Table 4. The significance of difference between the study arms (Tukey-Kramer post-hoc). Asterisk indicates significant difference ($p < 0.05$). Fr: freehand surgery; Pi: pilot guide protocol; Pa: partial guide protocol; Fu: fully guided surgery. AD: angular deviation; CGD:

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coronal global deviation; AGD: apical global deviation; VO: voxel overlap. Estimate: the least squares means of the pairwise differences; Adj. Lower and Adj. Upper: adjusted lower and upper 95% confidence interval limits for the least squares means of the pairwise differences; Adj.p: the adjusted level of significance for multiple comparisons; Effect sizes (Cohen's d) were calculated individually for each pair.





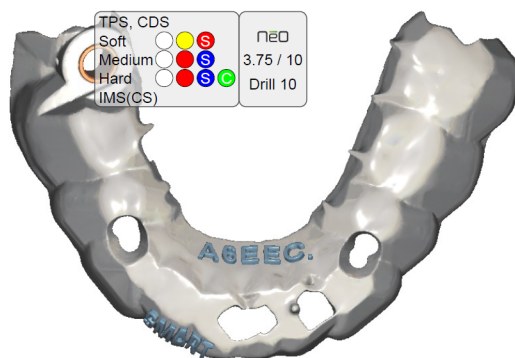
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Surgical Protocol

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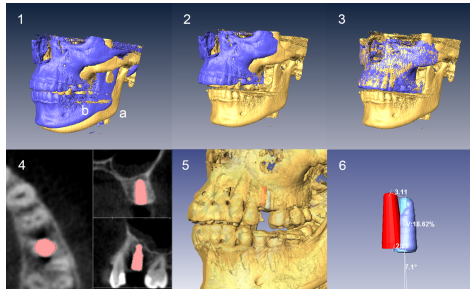
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Surgical Kit: Alpha-Bio Tec Guided Surgery Tool Kit (Full Sequence)



Start from the shortest drill and proceed stepwise until the drill length shown on the protocol.

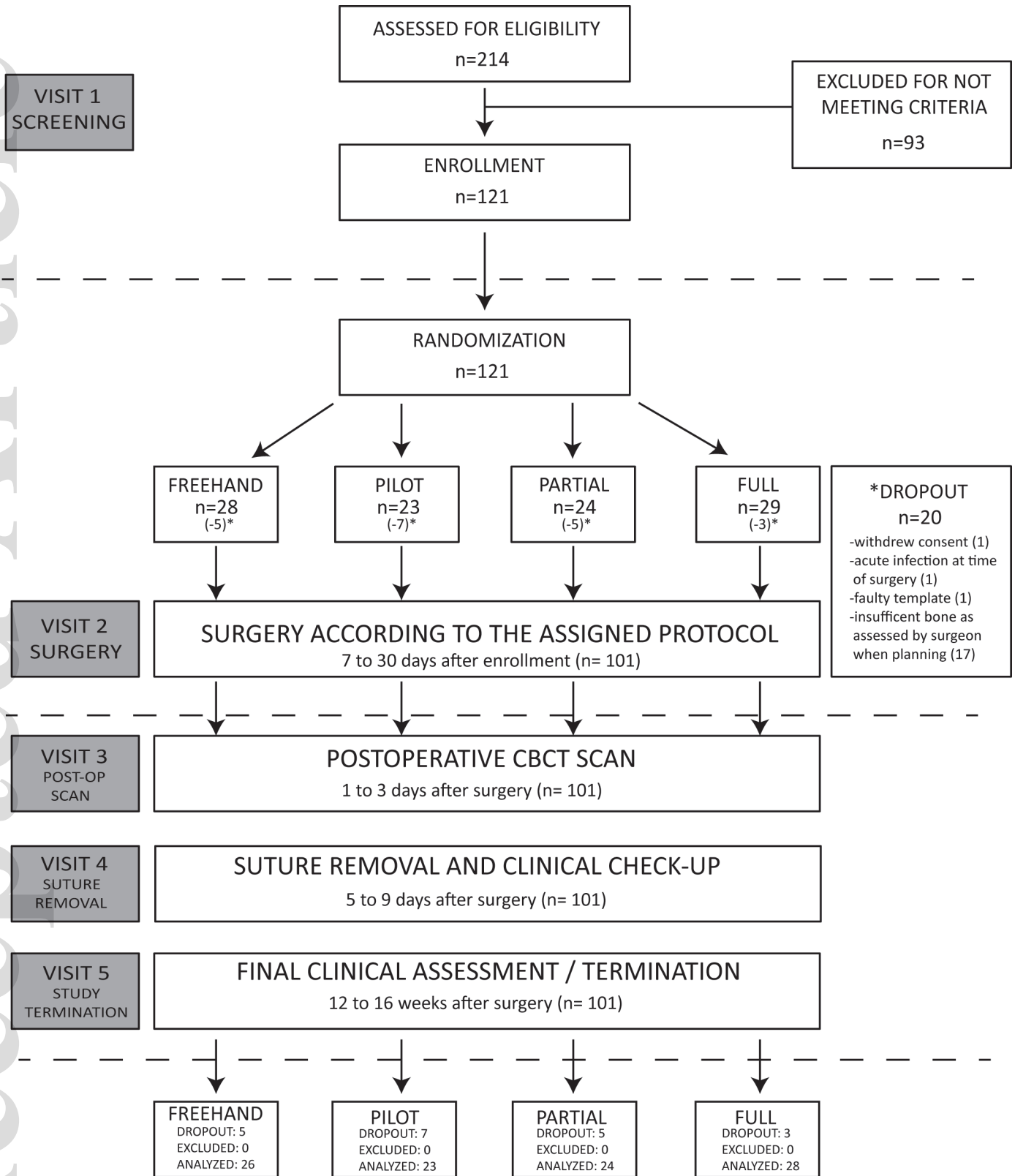
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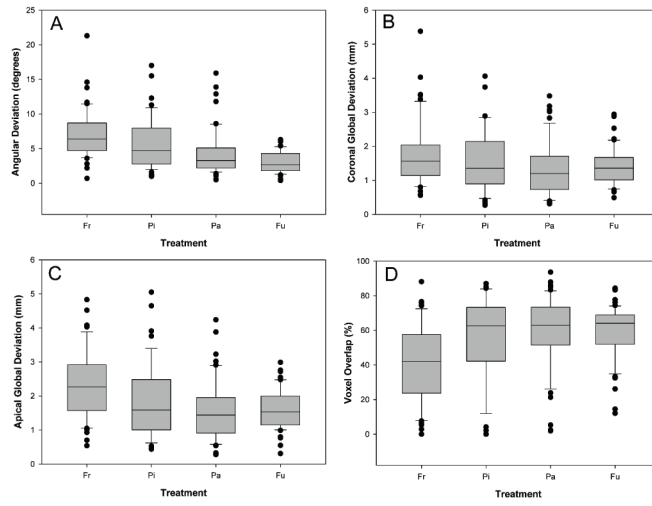
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