PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	3D-printed brace in the treatment of adolescent idiopathic scoliosis: A study protocol of a prospective randomized controlled trial
AUTHORS	Zhang, Youyu; Liang, Junyang; Xu, Nanfang; Zeng, Lin; Du, Chaojun; Du, Yaoxu; Zeng, Yan; Yu, Miao; Liu, Zhongjun

VERSION 1 – REVIEW

REVIEWER	Fabio Zaina ISICO (Italian Scientific Spine Institute), Italy
REVIEW RETURNED	01-Apr-2020

GENERAL COMMENTS	This is an interesting protocol for a clinical trial comparing different modalities of making braces for AIS. It's fair to compare new technology with standard of care to check for improvements in clinical approaches. There are some points in the protocol that need to be improved. First of all, it's not clear how TLSO are made. Are they traditional custom made realized using a cast or a CAD/CAM technology is applied with the preparation of a positive and then thermoforming? About compliance, it's now compulsory, to have realiable data, to use data logger. It isn't acceptable to rely only on reported compliance. The technology is available and it's cheap enough for a systematic use. Speaking about compliance, this relies much more on the team approach and the support given by doctors, physios and CPO than on the brace itself. This has been already demonstrated, together with the possibility to make patients were the brace 20-22 h per day. This should be clear and discussed. The statistical analysis plan could be improved and detailed. I suggest some relevant papers that should be added to the references https://www.ncbi.nlm.nih.gov/pubmed/32205704 https://www.ncbi.nlm.nih.gov/pubmed/22651570 https://www.ncbi.nlm.nih.gov/pubmed/29435499 https://www.ncbi.nlm.nih.gov/pubmed/22995590

REVIEWER	Sabrina Donzelli Isico Italy
REVIEW RETURNED	19-Apr-2020

GENERAL COMMENTS	There is a paucity of paper comparing bracing and 3D printed brace could represent the future of bracing. The topic is novel and interesting. I think that the project need more details and I suggest to consider to rethink on your main outcome. For data analysis the statistical analysis part should be improved and sensitivity analysis performed. You did'nt reported how you estimated the 20% of drop out and how are you managing missing data. Here are my comments: In the introduction line 40: The definition of 40 degrees threshold is not related to evidences about risks in adulthood but to an arbitrary decision made by some researchers to avoid loosing power in relation to the distrubiton of end of growth results in their population (Braist). Weinstein study reported that the risk of progression was present in 100% of cases of adults never treated observed until death if curves exceeded 50 degrees. For those with curves below 30 degrees no progression was observed. See also SOSORT guidelines to find referral for the threshold. AIMS: if you state that you are comparing clinical effectiveness than you need to add a measure of effectiveness as primary outcome, I agree with you that cobb angle has been given too much inportance, but for checking brace effectiveness we still need the curve measure. If you are comparing the impact on quality of life and satisfaction in different brace construction the outcome will be the one you choose, but I personally think it is a pity to loose the Cobb angle information. In this view I would consider also long term results, and not only short term as you planned. Please state it clearly that one your follow up will provide just short term results. Justify why you choose a short term follow up. Eligibility criteria: are including also secondary scoliosis ? Blinding: clarify how is it possible that the orthotist will be blinded to randomization, I am expecting that the brace is custom made on the patient after randomization? Interventions: please detail the clinical evaluation you are considering, and which treatment protocolos (dosage and general management, is physiotherapy provided ?) and radiographic protocols you are going to apply: xrays will be taken with or without the brace ? And how many hours after removal ? the number of hours after removal can significantly change results and is correlated to the real dosage of brace wear. I mean if the patient is wearing it 12 hours and perform the xray after 1 hour of break the results could be better than one patient wearing brace 23 hours and performing the xray after 12 hours of break. Primary outcomes: you are not considering Cobb angle among the primary outcome, please explain the reasons behind this choice. Compliance: please detail how are you going to measure it and if the patients will be aware of electonic monitoring or not, which device and how you'll manage those data. Can we consider drop out from the treatment as an adverse event, as it expose to higher risk of surgery ? Regarding x-rays: have you considered a maximum period of time between the xrays to be comparable ? In rapidly growing subjects a time exceeding the 3 months will not allow a fair comparison between baseline and in brace, as the curve could evolve significantly. In the curve progression outcome it is not clear if you are considering a binary outcome measure or a continuous measure? please clarify it.

	Regarding data management I congratulate with you, you are compensating the limitation correlated to open label design. Please state if the data manager will be blinded from allocation. Are you considering any interim analysis ? Sample size calculation: please justify why you define the risk for drop out as 20%. Statistical analysis: I strongly encourage you to consider a sensitivity analysis with a PP analysis including all the patients and considering the worst case scenario by including drop out as failures. I agree that patients reported outcome are important, but to avoid any confusion with effectiveness I would consider Cobb angle results. Patients wear plastic for long period and results in terms of prevention of problems in their adulthood is one of the outcome we use to convice them to adhere to such and an engaging treatment. Have you consider any measure for CPO satisfaction, I think it would be interesting to understang if 3d make easier to construct a brace. Considering the measure of quality of life it could be hard to use them as continuous measure, and there are some risks for an abnormal distribution of data, for which a t test could not be suitable. Further more I would consider a more clinically meaningful outcome, like Cobb progression over 5 degrees or surgery as a binary outcome for a logistic regression model to estimate and compare the odds for failure in the 2 intervention groups. The authors at line 20 page 12, are quoting Negrini's paper by using his name rather than surname.

VERSION 1 – AUTHOR RESPONSE

To Fabio Zaina (Reviewer 1):

1. First of all, it's not clear how TLSO are made. Are they traditional custom made realized using a cast or a CAD/CAM technology is applied with the preparation of a positive and then thermoforming?
For the technology to make TLSO, a CAD/CAM technology is applied with the preparation of a positive and then thermoforming, which was provided in our revised manuscript (Page 6 Line 9).

2. About compliance, it's now compulsory, to have realiable data, to use data logger. It isn't acceptable to rely only on reported compliance. The technology is available and it's cheap enough for a systematic use.
As per the reviewer's comment, data logger is compulsory for compliance monitoring. Temperature data logger (HOBO 64K Pendant-UA-001-64, Onset Computer) will be implanted in both 3D-printed brace and TLSO to log the date, time and temperature every 15 minutes. The raw data will be downloaded at follow-up and battery will be replaced every 6 months. Then it will be maintained for continuing data collection. Participants will be aware of the logger for monitoring the temperature of skin and so we can evaluate the fitness of brace. They will not be aware of the time logger. To reduce the chance of patient's awareness of time logger, self-reported compliance will also be required for patients or guardians via a time record software (Brace Former) in mobile phone, which can record the exact brace-wearing time every day and create a time curve automatically. Compliance outcome from data logger will be statistically analyzed finally. This approach was approved by our ethics committee. Moreover, temperature data logger (2.3in [5.8cm] x 1.3in [3.3cm] x 0.9in [2.3cm]) is small enough so as to not be obstructive to the patient. We made this clear in the revised manuscript. (Page 6, 'Interventions-braces')

3. Speaking about compliance, this relies much more on the team approach and the support given by doctors, physios and CPO than on the brace itself. This has been already demonstrated, together with the possibility to make patients were the brace 20-22 h per day. This should be clear and discussed.
We totally agree with the reviewer that compliance relies much on the team approach and the support given by doctors, physios and CPO than on the brace itself. We emphasized this in the 'Discussion' paragraph. We will also pay special attention to improve the compliance and insure that all patients in our study will be prescribed and guided by the same team. (Page11 L4-8)

4. The statistical analysis plan could be improved and detailed.
The statistical analysis plan was not explicitly stated in the initial manuscript and more details were improved in our revised manuscript. (Page 9-10 'Statistical analysis') Statistical analyses in this study will be performed following the intention-to-treat (ITT) analysis. ITT is usually required for Zelen's design. We will also perform a PP (per-protocol) analysis including all the patients and considering the worst case scenario by including drop out as failures. Results of PP analysis will be shared as supplementary materials finally. Patients in 3D group will be regarded as the participants in experimental group even when they choose TLSO. Curve progression, conversion to surgery and any adverse events will be measured as binary outcome. Compliance and immediate correction of Cobb angle of primary curve will be measured as continuous outcome in our design. Nonparametric test will be applied for HRQoL outcome including SRS-22 and BrQ. Nonparametric test or t test will be performed for continuous outcome according to the distribution. Chi-square test and logistical regression model will be used for binary outcome.

5. I suggest some relevant papers that should be added to the references
The papers suggested by reviewer are very helpful and we added them to the reference as per reviewer's suggestion. (Reference 3, 9, 30, 31)

To Sabrina Donzelli (Reviewer 2):
1. In the introduction line 40: The definition of 40 degrees threshold is not related to evidences about risks in adulthood but to an arbitrary decision made by some researchers to avoid loosing power in relation to the distrubiton of end of growth results in their population (Braist). Weinstein study reported that the risk of progression was present in 100% of cases of adults never treated observed until death if curves exceeded 50 degrees. For those with curves below 30 degrees no progression was observed. See also SOSORT guidelines to find referral for the threshold.
We agree with the reviewer about the relation between cobb angle degree and the risk of progression. A new statement was made clear in the first paragraph of 'introduction' (Page 2 Line 19-22). The risk of progression in adulthood increases with curve above 30°, as well as the risk of health problems and reduction of QoL, which are almost certain to happen with curve above 50° and then surgery should be recommended for AIS. This statement was based on the SOSORT guidelines as per reviewer's suggestion.

2. AIMS: if you state that you are comparing clinical effectiveness than you need to add a measure of effectiveness as primary outcome, I agree with you that cobb angle has been given too much inportance, but for checking brace effectiveness we still need the curve measure. If you are comparing the impact on quality of life and satisfaction in different brace construction the outcome will be the one you choose, but I personally think it is a pity to loose the Cobb angle information. In this view I would consider also long term results, and not only short term as you planned. Please state it clearly that one your follow up will provide just short term results. Justify why you choose a short term follow up.
As for the outcome, we agree with the reviewer that Cobb angle should still be given enough importance as a measure of effectiveness. Cobb angle progression over 5° of the primary curve will

be measured as primary outcome. This was made clear in our revised manuscript. (Page8 ‘Cobb angle progression’) Additionally, we moved ‘Incidence of adverse events’ to secondary outcome (Page 8 ‘Incidence of adverse events’). After discussion and rethink about the term of follow-up, we agree with the reviewer about long term results and we will maintain the follow-up to bone maturity. Risser sign of 4 (Risser 5 for boys) will be regarded as bone maturity endpoint in our research. Main curve >45° or surgery will be defined as failure endpoint. We made this clear in the revised manuscript and remove this point in the ‘strength and limitation’. (Page 4 Line 4-5)

3. Eligibility criteria: are including also secondary scoliosis?
Secondary scoliosis will be excluded from our study and we added this in the exclusion criteria. (Page 5 ‘Eligibility-exclusion criteria’)

4. Blinding: clarify how is it possible that the orthotist will be blinded to randomization, I am expecting that the brace is custom made on the patient after randomization?
According to the Zelen's design of the trial, patients randomized into the 3D group will make a decision between 3D brace and TLSO. Therefore, a patient receiving TLSO may either be from the 3D group but choosing a TLSO or from the TLSO group. As a result, the orthotist will be blinded to the result of randomization even when he or she is customizing the TLSO for the patient, according to the design of the trial. We made this clear in the revised manuscript. (Page 4 ‘Blinding’)

5. Interventions: please detail the clinical evaluation you are considering, and which treatment protocolos (dosage and geneal management, is physiotherapy provided?) and radiographic protocols you are going to apply: xrays will be taken with or without the brace ? And how many hours after removal? the number of hours after removal can significantly change results and is correlated to the real dosage of brace wear. I mean if the patient is wearing it 12 hours and perform the xray after 1 hour of break the results could be better than one patient wearing brace 23 hours and performing the xray after 12 hours of break.
The interventions were not explicitly stated in our initial manuscript and more details were added in the revised manuscript about the clinical evaluation, treatment and radiographic protocols. (Page 5-6, ‘Intervention-Assessment and management’) A form for clinical evaluation including heights, chest, shoulder and back asymmetric will be finished by clinician at admission and follow-up. Full-time-rigid-bracing (FTRB, 20-24 h per day) will be applied and prescribed for our participants. Physiotherapeutic scoliosis-specific exercise (PSSE) will be provided for all patients. X-rays including lateral and posteroanterior radiographs of the spine (including both full iliac crests) will be taken at the first in-brace and out of the brace at admission and follow-up. Generally, participants will not take off the brace until radiographic examination and wear it immediately after that.

6.Primary outcomes: you are not considering Cobb angle among the primary outcome, please explain the reasons behind this choice.
We agree with the reviewer that Cobb angle should be regarded as the primary outcome. We choose curve progression over 5° as the primary outcome. We made this clear in the revised manuscript. (Page 8, ‘Cobb angle progression’)

7. Compliance: please detail how are you going to measure it and if the patients will be aware of electonic monitoring or not, which device and how you'll manage those data.
As for the compliance monitoring, more details were added in the ‘Interventions’ as per the reviewer comment. (Page 6, ‘Interventions-braces’) Temperature data logger (HOBO 64K Pendant-UA-001-64, Onset Computer) will be implanted in both 3D-printed brace and TLSO to log the date, time and temperature every 15 minutes. The raw data will be downloaded at follow-up and battery will be replaced every 6 months. Then it will be maintained for continuing data collection. Participants will be aware of the logger for monitoring the temperature of skin and so we can evaluate the fitness of

brace. They will not be aware of the time logger. To reduce the chance of patient's awareness of time logger, self-reported compliance will also be required for patients or guardians via a time record software (Brace Former) in mobile phone, which can record the exact brace-wearing time every day and create a time curve automatically. Compliance outcome from data logger will be statistically analyzed finally. This approach was approved by our ethics committee. Moreover, temperature data logger (2.3in [5.8cm] x 1.3in [3.3cm] x 0.9in [2.3cm]) is small enough so as to not be obstructive to the patient.

8. Can we consider drop out from the treatment as an adverse event, as it expose to higher risk of surgery?
We totally agree with the reviewer that drop out from conservative treatment leads to higher risk of surgery. We added drop out as an adverse event in the revised manuscript. (Page 8, 'Incidence of adverse events')

9. Regarding x-rays: have you considered a maximum period of time between the xrays to be comparable? In rapidly growing subjects a time exceeding the 3 months will not allow a fair comparison between baseline and in brace, as the curve could evolve significantly.
Regarding the period of time between x-rays, we understand that time exceeding 3 months may have impact on the comparison between baseline and in brace for rapidly growing subjects. We set a 6 months interval in consideration of reducing radiation exposure, which was mentioned in the 2012 SOSORT and 2016 SOSORT consensus paper. This interval was also applied in the design of BrAIST, which was published on Spine in 2013. Additionally, regular telephone contact with all participants will be maintained by assistant once a month in our study. There will be fast channel in PUTH for emergency and any abnormal feelings needing to be solved by clinicians.

10. In the curve progression outcome it is not clear if you are considering a binary outcome measure or a continuous measure? please clarify it.
The measurement of curve progression outcome was not explicitly state in our initial manuscript. Curve progression over 5° will be regarded as binary outcome. This was made clear in the revised manuscript. (Page 8 'Cobb angle progression')

11. Regarding data management I congratulate with you, you are compensating the limitation correlated to open label design. Please state if the data manager will be blinded from allocation. Are you considering any interim analysis?
As for data management, data manager will be blinded from allocation, which is completed in outpatient by clinicians and researchers. We mentioned this in the revised manuscript. (Page 9 'Data management') Interim analysis is meaningful for the monitoring of brace treatment research. In our plan, reliability and validity of 3D printing brace were evaluated and verified in preliminary study, which has been performed previously. So, we are not considering interim analysis for the moment.

12. Sample size calculation: please justify why you define the risk for drop out as 20%.
For the rate of drop out in sample size calculation, it is just a maximumly estimated value in consideration of the poor compliance in adolescence and the rate of similar study in our hospital was lower than 20%. Except for detailed informed consent and careful management, we will also maintain regular telephone contact with all participants once a month to try our best to control the risk of drop out as low as possible.

13. Statistical analysis: I strongly encourage you to consider a sensitivity analysis with a PP analysis including all the patients and considering the worst case scenario by including drop out as failures. I agree that patients reported outcome are important, but to avoid any confusion with effectiveness I would consider Cobb angle results. Patients wear plastic for long period and results in terms of prevention of problems in their adulthood is one of the outcome we use to convice them to adhere to

such and an engaging treatment. Have you consider any measure for CPO satisfaction, I think it would be interesting to understang if 3d make easier to construct a brace.
Statistical analysis was not explicitly stated in our initial manuscript and more details were added in the revised manuscript as per reviewer's comment. (Page 9-10, 'Statistical analysis') ITT analysis is usually required for Zelen's design. We will also perform a PP (per-protocol) analysis including all the patients and considering the worst case scenario by including drop out as failures. Results of PP analysis will be shared as supplementary materials finally. Patients in 3D group will be regarded as the participants in experimental group even when they choose TLSO. Curve progression, conversion to surgery and any adverse events will be measured as binary outcome. Compliance and immediate correction of Cobb angle of primary curve will be measured as continuous outcome in our design. Nonparametric test will be applied for HRQoL outcome including SRS-22 and BrQ. Nonparametric test or t test will be performed for continuous outcome according to the distribution. Chi-square test and logistical regression model will be used for binary outcome.
Analysis for CPO satisfaction is really interesting. Moreover, we think it should be an independent research and we will pay attention to it in the future. Empirically, there are lower technical difficulty and time cost for 3D printing technology.

14.Considering the measure of quality of life it could be hard to use them as continuous measure, and there are some risks for an abnormal distribution of data, for which a t test could not be suitable. Further more I would consider a more clinically meaningful outcome, like Cobb progression over 5 degrees or surgery as a binary outcome for a logistic regression model to estimate and compare the odds for failure in the 2 intervention groups.
We agree with the reviewer's consideration for the hardness to use QoL as continuous outcome due to the risks for an abnormal distribution of data and then t test could not be suitable. Nonparametric test will be applied for QoL outcome including SRS-22 and BrQ. We made this clear in the paragraph 'statistical analysis' of revised manuscript (Page 10 Line 9-10). Meanwhile, we agree with the reviewer that cobb progression over 5 degrees or surgery should be regarded as binary outcome for a logistical regression model to estimated and compare the odds for failure in the 2 intervention groups. Curve progression, conversion to surgery and any adverse events will be measured as binary outcome. Chi-square test and logistic regression model will be performed for binary outcome. We made this clear in the revised manuscript (Page 9-10, 'Statistical analysis').

15. The authors at line 20 page 12, are quoting Negrini's paper by using his name rather than surname.
This was corrected in the revised manuscript. (Page 10 Line 31)