Reviewer #1: The iPSC technology is emerging as a new concept for diagnostics, drug development, bio-marker discovery and potential for therapeutics. In the present review, authors have summarised the use of such cellular technology to identify drug induced adverse events vis-a-vis developing personalised medicine. Authors have described and reviewed the potential use of iPSC technology in evaluating drug toxicity in various ailments. The review does provide a critical analysis of various pathological conditions where iPSC technology could make a difference in assessment and identifying the adverse events. However, there are number of limitations in the use of iPSC technology to achieve those goals at the moment because of the clonal variability, erasing of epigenetic memory of the parent cells, complexities of organ culture and faithfully gauging the outcomes etc and this review completely fails in addressing those issues. If authors are ready to incorporate a separate section of reviewing such limitations in using iPSC technology, this MS may be considered for re-review and publication

Reviewer #2: In this review, the authors present the multiple possibilities to address Adverse drug reactions (ADR) in a patient personalized manner using induced pluripotents stem cells (iPSC). The use of organoids and organ-in-a-chip are also presented. However, there is little emphasis in the use of these cells to address pedriatric specific problems. The organs discussed and modelized are very relevant for ADR. The authors often give too much information about the differentiation protocols used to differentiate the cells of interest from iPSC. However, this review is not a technical review and the authors do not point out the critical reagents or parameters in the protocols necessary to achieve the cells of interest. Thus, these descriptions appear like an overload of information. iPSC have been reprogrammed from centenarian persons and have acquired the same level of reprogramming as iPSC a derived from cells of juvenile subjects. Thus, the age of the original donor, may no longer be reflected after reprogramming. Please discuss this point as the cells derived from iPSC originated from adults or young subjects may respond in a same way to drugs. Page 12, the authors address the "interindividual difference" reflected in the iPSC. However, iPSC clones from the same patient may display differences. These intraindividual differences, which may be a foe to test drugs to ADRS are not mentioned in the review. Please discuss this point. The possibility to make direct conversions from somatic cells to cells of interest described in this manuscript exist, but this technology has not been presented here. Could this conversion approach present some advantages to iPSC for testing ADR? Please discuss

Reviewer #3: The so-called induced pluripotent stem cells are not same as real stem cells, they are unlikely to be used as stem cells for gene therapy or any medical research. It is now too late to stop spending time and money on these garbage cells- the so-called Induced pluripotent stem cells {J Biomed Res. 2015 Jan; 29(1): 1–2}.

Reviewer 1

We thank the reviewer for his comments and we agree with him about to add a separate section and a table regarding iPSCs limits. As required, we described the current limitations of iPSCs technology in the separate section attached.

Reviewer 2

The reviewer is right when saying that there is little emphasis in the use of these cells to address pediatric specific problems. However, the main reason about this is that, to our knowledge, there is a lack in the literature of works based on the study of ADRs using iPSCs technology applied to the pediatric field. We addressed this problem in the "adverse drug reactions in pediatric patients" chapter where we explained that, in general, ADRs in pediatric patients have not been studied so thoroughly as in adults. Moreover, we added a paragraph specifying pediatric specific problems that could be addressed by iPSCs technology, such as modeling of rare diseases and severe drug dependent toxicity of medications used mainly in pediatric patients (e.g. asparaginases).
We agree with the reviewer about the overload of information in the description of differentiation protocols and as requested we removed the technical parameters.

Reprogrammed iPSCs maintain an age related DNA methylation patters for a limited time. However, as reviewer 2 said, the age of the donors may no longer be reflected in iPSCs, in particular after several passages due to the erase of epigenetic memory. However, it is important to highlight that parental cells of old donors are subjected to a higher frequency of genetic aberration with a correspondent increased of DNA mutations in the derived iPSCs associated with cellular defects and cancer. Therefore, to address the question, drugs could respond differently in iPSCs from centenarians with respect to young subjects in terms of DNA mutations related to the age as described in the new added limit section. It is important to keep in mind that every case is different and related to the specific drug and mutation.
As about clonal variability we addressed the problem in the new "limits of iPSCs" chapter concluding that there is an open debate on this aspect and given the contrasts still present, the intra-patients variability between different iPSCs clones of the same donor should be investigated and it is advisable to deep analyze the genetic and epigenetic features of the clones generated. We discussed also, as requested, the problems related to clonal variability and the setting up of a representative patient-specific model. For sure, chromosomic aberrations, alterations in differentiation efficiency and variability in DNA methylation profiles should be analyzed in different clones generated. Also the sensitivity to the drugs of interest should be analyzed in the different clones to exclude a variation in the response.

Reviewer 3

We appreciate the consideration that the reviewer gave to our manuscript but we ask you not to include his revision in the evaluation of our paper. Indeed the reviewer harsh comments are not specific to our manuscript and seems biased against the induced pluripotent stem cells technology. The reviewer seems not to consider authorative scientific works and ongoing projects supporting the validity of induced pluripotent stem cells as both a ground-breaking base for pre-clinical models to study disease (Li and Izpisua Belmonte, NEJM 2019) and drugs' effects (Shi Y et al., Nat Rev Drug Discov. 2017) and as a therapeutic approach (https://www.nature.com/articles/d41586-018-07407-9). While we acknowledge that the induced pluripotent stem cells technology is highly innovative, being developed just slightly more than 10 years ago (https://www.cell.com/iPSC), and that it has still to fulfill its potential and promise, both as a regenerative medicine intervention and as a pre-clinical model, we think there is great support on the meaning fullness in research efforts using this approach. Indeed, more than 10% of the articles published in your Journal (37 out of 351) have induced pluripotent stem cells has a topic/key word. Moreover, the reference cited from the reviewer is from a Journal still with no impact factor. Anyway, we added a section about iPSCs technology.
The reviewer may address to the use of an alternative to iPSCs in the study of ADRs. A possible alternative to this technology could be the use of embryonic stem cells (ESCs). However, there are several powerful advantages in using iPSCs with respect to ESCs. Two important point to discuss are the ethical concern related to the embryo destruction and that ESCs are a limited source with respect to iPSCs. However, so far, the debate if ESCs and iPSCs are similar or different is still open and studies have conflicting conclusions regarding this aspect. DNA methylation patterns and epigenetic memory are two key points of this discussion. Overall, based on the current knowledge iPSCs seems to be more useful to study ADRs with respect to ESCs.