

# Applied biostatistics in clinical trials for 15-year-old pupils

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## Abstract

It is important for young people to be aware of job profiles and activities in the professional world. Bringing the education system closer to the professional world is vital for them to make decisions about their academic and professional futures. Programs developed to connect 15-year-old students who in Spain are in year 4 of their Compulsory Secondary Education, and Research Support Units within the Health Research Institutes of the Hospitals and the Clinical Research Support Platforms of the Carlos III Institute of Health are a good opportunity to highlight the role of biostatistics in clinical trials. The aim of this article is to share the outcomes of and learnings from an interactive workshop for 15-year-old students on biostatistics and clinical trials conducted within the 4°ESO + Empresa program and directed by the Scientific Support Unit of the Health Research Institute of Hospital 12 de Octubre in Madrid, Spain.

## KEYWORDS

biostatistics, randomized controlled trial, teaching statistics

## 1 | INTRODUCTION

Bringing the education system and the professional world closer together is vital to better prepare young people to make decisions about their academic and professional futures. In order to help students in Compulsory Secondary Education (ESO), Baccalaureate, and Vocational Training choose their future education, there are different formats: Conferences, for example, “El PAÍS con tu futuro” [6], conducted by experts from different disciplines and fields that discuss the job profiles and professions expected to see the highest demand in the future; Open days and workshops, for example, the 4°ESO + Empresa program [5], which was developed by the Ministry of Education of the Community of Madrid (Spain) and consists of visiting the facilities of a company over 3 and 5 consecutive

days to observe how business is carried out, where participants even have the chance to participate in the development of basic tasks or functions during the visit. All the programs emphasize educational and pedagogical aspects, as well as the voluntary nature of the students and the centers: institutions, bodies, business organizations, small and medium-sized enterprises (SMEs), and non-profit organizations. Similar initiatives are carried out periodically in the scientific field with different objectives, including highlighting the importance of research and the work of research personnel for the well-being of society, bringing science closer to the public of all ages, developing a taste for scientific knowledge, and encouraging the participation of citizens in scientific issues through activities. Science Night and Science Week with national and European activities are particularly noteworthy [3,15].

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Health Research Institutes (HRIs) in Spain are dedicated to the development of the highest quality research and innovation activities with the aim of transferring results to clinical practice as much and as fast as possible, helping to improve patients' state of health. The HRIs are functional structures of multidisciplinary and translational biomedical research oriented toward basic, clinical, epidemiological, and health services research, and are associated with research networks, research support platforms, and universities, among other entities. Of particular note are the Scientific Support Units and Clinical Research Support Platforms of the Carlos III Institute of Health (ISCIII), such as the Spanish Clinical Research Network (SCReN) [14], within the HRI. They include professionals with different academic backgrounds, professional profiles, and activities: methodology, informatics, bioinformatics, clinical research associate (CRA), data management, data science, and biostatistics.

Biostatistics plays a relevant role in the Scientific Support Units of the HRI and the SCReN platform associated with the HRI, helping to establish the association between clinical practice and clinical research under three pillars: scientific support to individuals associated with the HRI requesting this help, teaching, and the development of their own lines of research. The quality of the teaching and consultancy activities will significantly depend on this last activity. Focusing on the biostatistical support activity, the elaboration of the methodological design would entail [12], among others, the establishment of conceptual and operative hypotheses, the determination of the sample size, as well as the elaboration of the statistical analysis plan, the statistical programming and code validation, data analysis, the presentation of results, and communication. This activity within the framework of the Scientific Support Units of the HRI and the SCReN platforms associated with the HRI translates into the construction and development of research projects, observational studies, and randomized controlled trials (RCTs).

The aim of this article is to share the outcomes of and learnings from an interactive workshop for 15-year-old students on biostatistics and clinical trials conducted within the 4°ESO + Empresa program and directed by the Scientific Support Unit of the Health Research Institute of Hospital 12 de Octubre in Madrid, Spain.

## 2 | MATERIALS AND METHODS

### 2.1 | Program design and setting

The 4°ESO + Empresa program was held at the HRI of Hospital Universitario 12 de Octubre (i + 12) for 5 hours a day during 4 days in April 2023. First day: welcome and

the Ethics Committee for Drug Research (CEIm); second day: clinical research and RCT in oncology, cardiology, pathology, and pharmacy services; third day: infection disease and AIDS unit; last day: Data Science Unit and Scientific Support Unit.

The workshop presented by the Scientific Support Unit of i + 12 lasted 2 hours and consisted of the following: (a) presentation of the Scientific Support Unit: structure, activity, and professional profiles (30 minutes); (b) workshop on biostatistics applied to an RCT (50 minutes); (c) presentation of a real RCT (30 minutes). This article discusses a biostatistics workshop that focused on RCT.

### 2.2 | Participants

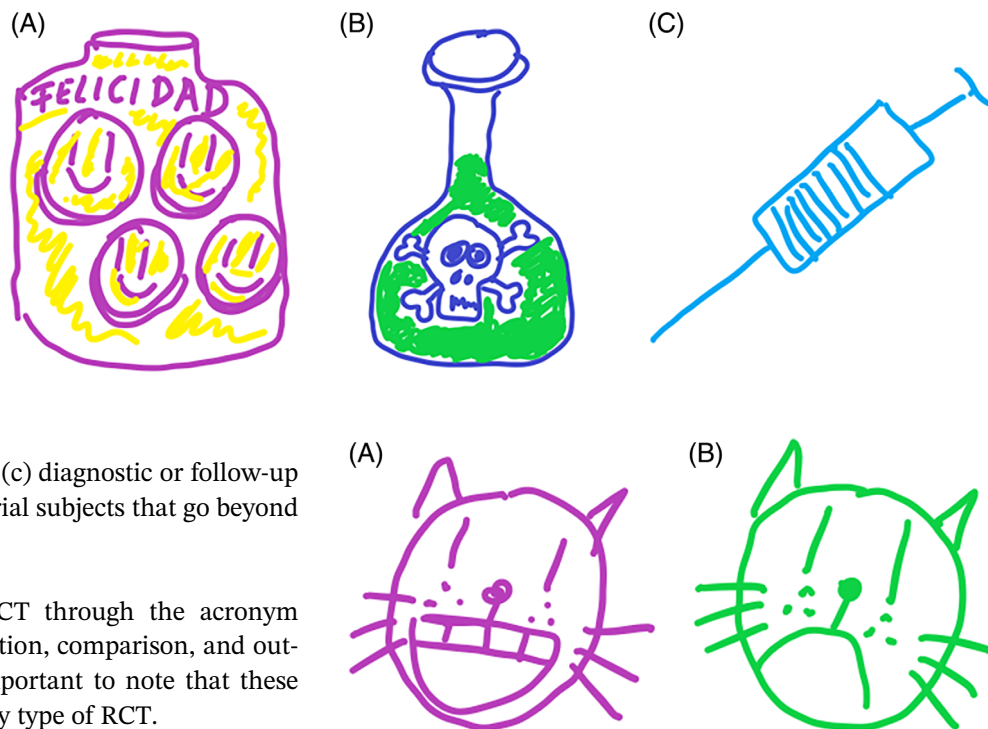
The HRI of Hospital Universitario 12 de Octubre (i + 12) offered educational activities within the 4°ESO + Empresa program for the 2022–2023 school year. The students of the educational centers supported with public funds of the Community of Madrid requested voluntary participation in the activities. Students are selected based on the number of places offered in each activity, a scale established by the Department of Education of the Community of Madrid, and characteristics and preferences of each student. Finally, a group of students was made up of 11 students who were approximately 15 years old, and at the time of the activity, they were in year 4 of ESO in the Community of Madrid, Spain. The equivalent of year 4 of ESO in the English education system is Key Stage 4 for pupils.

### 2.3 | Description of the biostatistical workshop for a clinical trial

The following section shows the notes for facilitators, including how the workshop was explained to the students. The activity was structured around 13 slides, where the first (Slide 1) and the last (Slide 13) were the opening and closing slides of the workshop (Appendices S1–S4):

Slide 2: Definition of an RCT based on Royal Decree 1090/2015, of 4 December, which regulates clinical trials on medicines, the Medical Research Ethics Committee, and the Spanish Clinical Studies Registry [2]. An RCT is defined as a clinical study that meets any of the following conditions: (a) The trial subject is pre-assigned to a particular therapeutic strategy, which is not part of the usual clinical practice of the Member State at hand; (b) the decision to prescribe the medicinal products being researched is taken together with the decision to enroll

**FIGURE 1** Figure of treatments: (A) sweet syrup, (B) bitter syrup, and (C) intravenous medication. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



the subject in the clinical trial; (c) diagnostic or follow-up procedures are applied to the trial subjects that go beyond usual clinical practice.

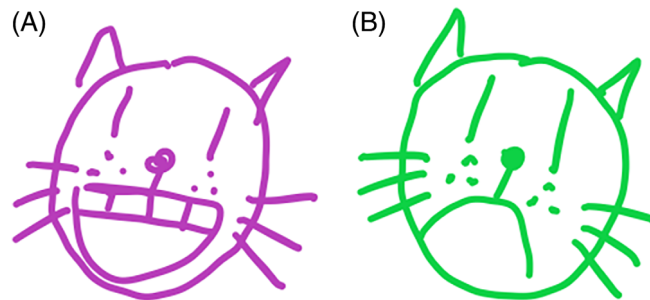
Slide 3: Description of an RCT through the acronym PICO [8] (population, intervention, comparison, and outcome): In this slide, it was important to note that these words can be used to define any type of RCT.

Slide 4: Example 1 was presented and defined according to the PICO structure. The population was healthy and under 18 years of age. The students present were the chosen participants. What a coincidence that we had N participants! They also needed to sign the informed consent form, which was reviewed later by the CRA. And who is the CRA? CRA [7] is the person who oversees the progress of a clinical trial and ensures that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and the applicable regulatory requirement(s). The existing treatments were as follows: Intervention, which represents the sweet syrup (Figure 1A), and Comparison, which represents the bitter syrup (Figure 1B). The drawings were presented to the participants. Finally, the outcome to be measured was defined: as happiness after 10 minutes.

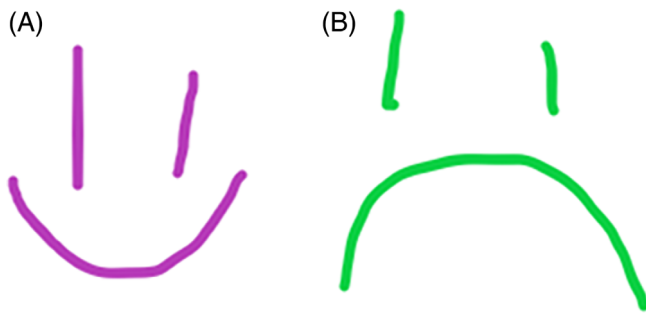
Slide 5: The concept of blinding was defined [11], that is, the process by which participants, healthcare providers, and researchers, including those evaluating the results, are not aware of the allocation of treatments after participants have been included in the study. Emphasis was placed on the open-label nature of the RCT conducted in the workshop, where participants were aware of their assigned treatments. It was indicated that this was a scenario similar to what can occur in surgical RCTs.

Slide 6: The concept of random allocation was defined, that is, a process that allocates participants to the intervention or control group by chance [11]. Avoided addressing the concept of random sequence concealment and

**FIGURE 2** Clinical outcome: happiness at 10 minutes through Petey's face. Petey's face was made following the instructions of Dav Pilkey's series "Dog Man." [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



how it is different from blinding. The first two of the three benefits of randomization were listed [13]: (a) the incorporation of randomization provides unpredictability in treatment assignments, thereby mitigating selection bias; and (b) randomization tends to ensure similarity in the treatment groups on known and unknown confounders. The third point, which states that the act of randomization itself provides a basis for inference when random sampling is not conducted from a population model, was considered to be beyond the knowledge of 15-year-old students. Then it was stated that they would be randomly assigned to a treatment: half would be assigned the sweet syrup and the other half the bitter syrup, at a ratio of 1:1. To illustrate randomization in real time, colored marbles were used. If chewy candies had been used, it would be necessary to take into account people with coeliac disease, gluten-free diets, food allergies, for example, milk, eggs, or nuts, as well as food intolerances, and to present the chewy candies in a sealed bag showing the list of ingredients. In their presence, N/2 violet and N/2 blue marbles were selected and placed in an opaque bag. Each subject was asked to take 1 marble out of the bag. They were given treatment according to the color of their marble: either the violet sweet syrup sheet (Appendix S2A) or the blue bitter syrup sheet (Appendix S2B). No one took syrup; medication was administered visually through the sheets. At this point,



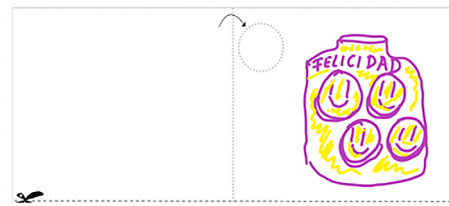
**FIGURE 3** Clinical outcome: happiness at 10 minutes through a bold drawing. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

they were told that the sheet they received was the case report form (CRF). The definition was given, that is, CRF [7] is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject. The data management is responsible for developing the CRF. Technically, intervention was carried out visually through the CRF. The number of participants was an odd number; the fact that biostatistics also contemplates the possibility of working with missing data was discussed. In the case of an even number of participants, the comment would have been omitted.

Slides 7 and 8: The outcome to be studied was described: happiness at 10 minutes reported as happiness (Figure 2A) or no change (Figure 2B). While being shown the figure, the students were told that the cat is called Petey and is one of the characters in Dav Pilkey's series "Dog Man" [4,9]. Dav Pilkey is the creator of *Captain Underpants* [4,10]. The students were then asked to draw their state of happiness on the inside of the CRF. If they were happy, they were to draw Petey's smiling face (Figure 2A) and if they were unchanged, they were to draw Petey with a sad face (Figure 2B). Those artists who were less bold could always have drawn their state as in Slide 8: Figure 3A reflects happiness and Figure 3B indicates no change. When everyone had filled in their emotional state, the CRFs were collected.

Slide 9: Example 2 was presented and defined according to the PICO structure [8]. They were reminded that they were participating in a new study of a healthy population and were shown the intervention, intravenous sweet syrup, and the Comparison, intravenous bitter syrup. They were told that the outcome to be measured is happiness at 10 minutes. They were then given the new CRF (Appendix S2C). No one was jabbed; medication was administered visually through the CRFs. The importance of signing the informed consent form was again explained to them and these forms were reviewed by the

Cut out the CRFs of APPENDIX 3



Fold the CRFs



Add consecutive numbers from 1 to N for CRFs of each example



**FIGURE 4** Instructions for preparing the project's case report form (CRF). [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

CRA. The CRFs were numbered before they were handed out. This linked the assigned treatment with the random sequence used (Appendix S3).

Slide 10: On this slide, we stopped the game and asked the following questions: (a) Is there blinding? (b) What about random allocation? Students were given time and their responses were heard. This allowed us to correct the concepts addressed. For the second question, the random allocation table was displayed, indicating that each CRF number corresponds to a line of the random sequence, which in turn corresponds to the assigned treatment. We added that the task of generating the random sequence is specific to the biostatistician and is done through a bag of colored marbles called statistical programming.

Slide 11: Next, they were instructed to fill in their state of happiness on the inner sheet and the CRFs were collected.

Slide 12: The measurement used to evaluate the treatment effect was defined. To this end, relative risk (RR) was used by generating a contingency table that shows the relationship between the treatment and the development of happiness as a percentage ratio. A contingency table identical to that of Slide 12 was then drawn on the board and the number of smiling faces by treatment for Examples 1 and 2 was counted and the RR was calculated. The concept of confidence interval was not explained in detail, only the point estimate. The fundamental role of the biostatistician in the analysis planning, the data analysis itself, its subsequent presentation, and explanation through the reports was explained in detail. Once again, pupils were asked to reflect. To this end, they were asked, in view of the results, whether they believe that knowing the treatment they received, in other words,

the lack of blinding, might have modified their state of happiness after 10 minutes. After asking this question, it was better to remain silent and allow for reflection.

## 2.4 | Activity elements

The activity required a projector, a board for writing, paper to be used as a CRF and a pen. The CRFs (Appendix S2) were prepared before the activity. The following steps were carried out: (a) print a number of CRFs equal to  $N/2$  participants (Appendix S2); (b) cut out the CRFs; (c) fold according to the instructions; (d) add consecutive numbers from 1 to  $N$  for the open-label CRFs; (e) add consecutive numbers from 1 to  $N$  for the double-blinded CRFs related to the random allocation list; preparation example Figure 4 and if you are going to use Appendix S3, remember not to jab anyone. It is just a game.

## 3 | RESULTS

### 3.1 | Survey of the 4°ESO + Empresa program

A general survey was carried out on the 11 students enrolled in the activity carried out within the 4°ESO + Empresa program of the HRI of Hospital 12 de Octubre ( $i + 12$ ). The survey consisted of 18 questions related to the duration and schedule, compatibility between stays and studies, academic training improvement, and assessment of the stay to make decisions about their academic and professional futures: 2 out of 11 indicated “sufficient,” 8 out of 11 indicated “good,” and 1 out of 11 indicated “very good,” organization and relationship with the company, information offered by the educational center about the company, recommendation of the stay, expectations met, degree of satisfaction, negative, positive, and improvement aspects.

The students mentioned that they liked the workshops, visits to laboratories, and hospital facilities the most, while they found the lectures to be the least enjoyable. One person specifically highlighted the activities of the last day with a smiling face (Figure 3A), and two more surveys included smiling faces associated with the word “thank you” (Appendix S4).

### 3.2 | The biostatistical workshop for a clinical trial

Eleven people were included in two RCTs: Examples 1 and 2.

In Example 1, five people were treated with sweet syrup and six with bitter syrup. Of the patients, 5 out of 5 (100%) who took a sweet syrup described happiness 10 minutes later, while 3 out of 6 (50%) who took bitter syrup described happiness. That is, for every one happy person at 10 minutes of those taking bitter syrup, there are two happy people at 10 minutes who took sweets syrups. RR equals 2. Of the patients, two people taking the sweet syrup drew Petey with a happy face, and in three people with the bitter syrup, one of them drew a sad face.

In Example 2, five people were treated blindly with the intravenous sweet syrup and 6 people were treated blindly with intravenous bitter syrup. Of the patients, two out of five people (40%) who received intravenous sweet syrup described happiness 10 minutes later, while two out of six people (33.3%) who received intravenous bitter syrup reported happiness 10 minutes after administration. That is, the probability of being happy after 10 minutes is 1.2 times higher when receiving the intravenous sweet syrup than when receiving the intravenous bitter syrup. Only one person drew Petey's smiling face and had the bitter syrup. The visual overviews of results from clinical trials, examples 1 and 2, were produced aiming to make essential clinical findings accessible (Figure 5).

## 4 | DISCUSSION

Activities aimed at young people to bring the education system closer to the professional world related to biostatistics should be informative and focused on play. During the activity, it was important to clarify the definition of RCT, its characterization through the acronym PICO, the concepts of the CRFs, random sequence and random allocation, blinding and relative risk, as well as the job profiles involved in an RCT within the Scientific Support Units of the HRI and the SCReN platform associated with the HRI.

The incorporation of randomization using colored marbles adds and shows unpredictability in treatment assignments. The students understand the randomization concept [13] in their own play, and questions about known and unknown confounders, that is, baseline happiness of each student, could reinforce the idea about the similarity of baseline characteristics between groups [13]. Future workshops could include the following steps: add one more slide to slide 4 where the participation of the students in the clinical trial could be indicated; add the explanation about the “informed consent form”; introduce the concept of CRF and give a first numbered CRF where the student should record “baseline

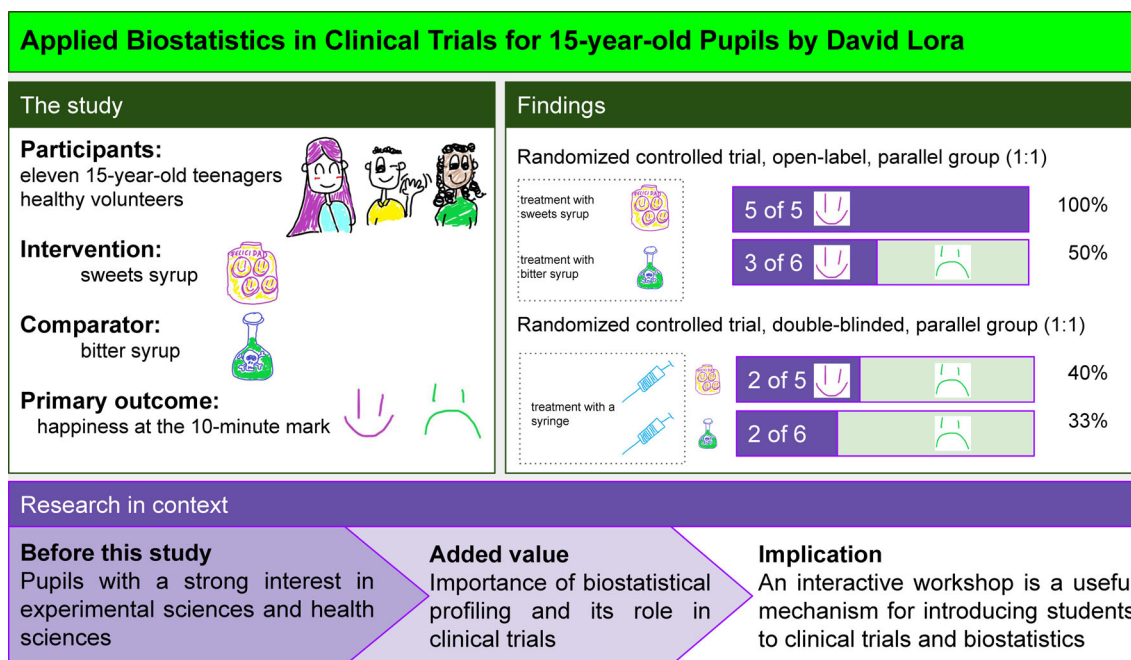


FIGURE 5 Essential findings and visual abstract of biostatistical workshop. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/jesl.12358)]

happiness of each individual” inside, using a visual analogue scale between 0 and 10, or a Likert scale or similar. It is important to demonstrate whether individuals who were initially unhappy upon arrival may or may not become happier after receiving treatment. This would also reinforce the idea of similar characteristics. Likewise, the clinical outcome could be modified to include a Likert scale, visual analogue scale, or continuous variable. Continuous variables offer all the information without the dangers of dichotomizing the variables [1] and would coincide with the baseline way of evaluating students if the new slide was incorporated. This modification would imply that the student must number the second CRF with the same number as the first.

In my opinion, each concept can be further elaborated and developed with its various nuances, but it is preferable to point out the definitions in an assertive way, associating the concepts with the images. Too much information on each concept could be detrimental to the development of the workshop. On the other hand, student participation is fundamental, as is their thinking aloud and active listening. Debate, should there be any, is to be allowed. In addition, the activity coordinator should have a friendly attitude to hold participants' attention.

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#### REFERENCES

1. D. G. Altman and P. Royston, *The cost of dichotomising continuous variables*, *BMJ* **332** (2006), no. 7549, 1080. <https://doi.org/10.1136/bmj.332.7549.1080>.
2. *Real Decreto 1090/2015, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos*. BOE-A-2015-14082, available at <https://www.boe.es/buscar/doc.php?id=BOE-A-2015-14082/>.
3. British Science Week, available at <https://www.britishscienceweek.org/>.
4. Dav Pilkey, available at <https://pilkey.com/>.
5. EducaMadrid. *4eso+empresa*, available at <https://www.educa2.madrid.org/web/4eso-empresa>.
6. El País Sociedad. *El País con tu futuro*, available at <https://elpais.com/sociedad/2022-12-23/el-pais-con-tu-futuro.html>.
7. European Medicines Agency (EMA). *ICH E6 (R2) Good clinical practice—Scientific guideline*. 2018, available at <https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline>.
8. J. P. T. Higgins, S. Green, and Cochrane Collaboration, *Cochrane handbook for systematic reviews of interventions*, Cochrane Collaboration, 2011, available at <https://training.cochrane.org/handbook>.
9. D. Pilkey, *Dog Man*, Scholastic, 2017, available at <https://www.scholastic.com/site/pilkey/dav-pilkey-at-home/dog-man-series.html>.

10. D. Pilkey, *Captain underpants: The adventures of captain underpants (colour edition)*, Scholastic, 2018, available at <https://www.scholastic.ca/books/view/the-adventures-of-captain-underpants-colour-edition>
11. S. J. Pocock, *Clinical trials: A practical approach*, John Wiley & Sons, Ltd, 1983, available at <https://onlinelibrary.wiley.com/doi/book/10.1002/9781118793916>
12. S. Porkess, *Statistics and clinical trials: It's all about the design*, *Teach. Stat.* **45** (2023), no. 1, 27–35. <https://doi.org/10.1111/test.12325>.
13. W. F. Rosenberger, D. Uschner, and Y. Wang, *Randomization: The forgotten component of the randomized clinical trial*, *Stat. Med.* **38** (2019), no. 1, 1–12. <https://doi.org/10.1002/sim.7901>.
14. SCReN. *Spanish Clinical Research Network ISCIII*, available at <https://www.scren.eu/>.
15. Spain.info. *Science Week. Madrid*, available at <https://www.spain.info/en/calendar/science-week/>.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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