Research Square

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Determination of child, young person and adult research priorities in Osteogenesis Imperfecta using a multinational focus group approach

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Abstract

Background

The research priorities of children and young people (CYP) and their families with chronic conditions may be different from those perceived by the healthcare professionals supporting them. We aimed to determine the priorities for research of CYP with osteogenesis imperfecta (OI) and their parents, and also to determine what tests and assessments they would be willing to undergo in support of meeting those priorities.

We undertook focus group sessions of six to eight CYP aged 11-18 years and parents with OI separately in seven different countries. Groups were led by a local investigator with free discussion and directed as detailed below. Each group met for up to 1.5 hours to answer the specific questions “what are the most important research outcomes for you?”; “what would you be willing to do to achieve those outcomes?”; and ”what type of study would you be willing to take part in?” Ideas were captured on flipcharts for 30 minutes, then rated using green (support) or red (oppose) stickers.

Results

There were 20 distinct suggestions made by CYP and 41 by adults. The research outcome priorities grouped into six major themes; bone-specific treatments, including surgery; identification of issues with non-skeletal systems; treatments to strengthen bones and/or reduce fracture risk; improving lifestyle; testing; and basic or education research (CYP) or basic and health services research (adults). The most supported outcome for CYP was treatment to strengthen bones and/or reduce fracture risk; for adults improving lifestyle. Interventions to measure body size, bone density, take radiographs, have blood tests and answer questionnaires were supported by at least 90% of CYPs. Adults were generally less keen on tests. CYP were twice as likely to agree to take part in a comparator (67% vs 33%), open label (61% vs 28%), or placebo-controlled (25% vs 12%) study.

Conclusions

CYP and adult priorities for research differ. Children are more willing than adults to both participate in studies and to undergo relevant procedures in pursuit of those priorities. Research priorities for CYP with OI should be considered separately from those of adults when designing intervention studies.

Background

Osteogenesis Imperfecta (OI) is a disease with varying severity affecting the physical, social and emotional well-being of the individual and their family. It is an hereditary condition affecting approximately 1 in 10,000 births with at least five distinct phenotypes (1) and mutations in more than 20 different genes identified as causative. (2) Clinical manifestations include: low bone mass; recurrent fractures, often with minimal trauma; bone pain; varying degrees of short stature and deformity; muscle

weakness; hearing loss; scoliosis; kyphosis; skull base deformity and respiratory failure in the severest types can be lethal.(3)

There is broad agreement about the crucial role of patient involvement in research with the consequent benefit of patient engagement in the planning and execution of research, resulting in improved translation of research into clinical care. Patient engagement can be broken down into three phases; preparatory phase (agenda setting, prioritisation of research topics and funding), execution phase (study design and procedures, study recruitment, data collection, and data analysis), and translation phase (dissemination, implementation, and evaluation)(4)

New therapeutics are emerging for OI; some translated from approaches in adult osteoporosis, (5) some with a specific targeting of OI. (6, 7) Existing treatments, primarily using bisphosphonates, have had equivocal results in reducing fracture frequency, (8, 9) with clear effectiveness demonstrated only for oral bisphosphonates in the more mildly affected individuals.(10, 11) The results from the metanalyses may be in part due to the difficulty of undertaking controlled trials of intravenous therapy, particularly in children, and in addition when there is both a perceived efficacy (from a patient perspective) that leads to an pronounced unwillingness to participate in placebo-controlled studies when there is a high risk of fracture in the untreated population. Neridronate is licensed for the treatment of OI, based on controlled (but unblinded) studies(12, 13), but only in Italy. As new therapeutics emerge and compete with the established treatments, healthcare systems are likely to ask what the benefit to patients is, whether the new treatments are more likely than bisphosphonates to meet the patients' needs, and thus what those perceived needs are. Whilst fracture risk reduction is always the primary endpoint for phase III efficacy studies in OI, patients with this multisystem disorder may have other needs and priorities that also need to be considered and addressed.

Focus groups involve a moderated, planned discussion on a specific topic of interest. They usually involve six to eight people(14), although four to six may be more preferable when working with children. The sample is purposive, but not always representative. The goal of the focus group is to elicit as many ideas as possible about a chosen topic, enabling all participants to feel comfortable and their voice to be heard. Predefining the structure, with a set of semi-structured questions can prevent loss of direction and aid moderation. Bloor et al(15) state the moderator should attempt to facilitate a group and not control it; the interaction of some groups can be distorted by too much external control and can lead to bias. Ideally, some individuals will stimulate the thoughts and opinions of others, leading to deeper understanding.

The primary aim of this exercise was to assess the main needs and thus research priorities for children and young people (CYP) as well as adults with OI through the use of focus groups. Secondary aims were to identify the processes and procedures they would be willing to undergo in pursuit of those priorities and ascertain their willingness to participate in prospective research studies of different types.

Methods

We undertook focus group sessions in CYP and adults with OI separately in seven countries for CYP and in eight countries for adults; Belgium, Chile, China (Hong Kong), France, Germany, Italy, the Netherlands and Russia; Germany did not participate in the CYP focus groups. Groups were led by a local healthcare professional investigator with some free discussion and some directed questions as detailed below. The individual centres were approached through personal contacts made during a previous piece of work around an international consensus guideline for occupational and physio-therapy for children with OI, through contacts within the European Reference Network for Rare Bone Diseases (ERN BOND), and through contacts of the Care4BrittleBones Foundation. Criteria for participation were set with a target group size of six to eight individual participants. A teleconference was held with each of the focus group leads to ensure a consistent approach. The protocol complied with all local and national governance rules in each country and was approved by the relevant authorities in each country. The study was not registered as a clinical trial as it did not fall within the World Health Organisation definition which is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes".

Each participant had a clinical diagnosis of osteogenesis imperfecta; each child participant was aged 11–18 years. Each group met for up to 1.5 hours to answer the specific questions “What are the most important research outcomes for you?” and “What would you be willing to do to achieve those outcomes?” A list of possible procedures was provided as follows in order of increasing invasiveness: questionnaire; interview; focus group; measurement of height and weight; plain radiographs (stated as “x-rays”); dual energy x-ray absorptiometry (DXA scan); urine sample; blood test; skin biopsy; bone biopsy during surgery.

Both CYP and adult participants were also asked whether they would consider participating in an interventional clinical trial, and if so what sort: comparator against existing treatment; open label study of a new treatment; randomised placebo-controlled trial of a new treatment; trial of a new surgical procedure. Participants were also asked what factors would be likely to influence their decision on whether to participate or not.

Ideas were captured on flipcharts for 30 minutes and then rated using stickers - green for the outcomes individuals wished to support, red to assign to the procedures they didn’t like. The flip charts were photographed, the scoring (using the red and green stickers) summarised and where English was not the first language, all anonymous information was translated into English. This anonymous information was then collated and sent back to the lead investigator.

Each focus group was audio recorded and the recording transcribed by an independent transcription company; participant pseudonyms were used in order to differentiate participant contributions. Translation to English was undertaken with the support of local support groups and ERN BOND members.

Data are presented as collected without statistical analysis.

Results

Twenty different themes emerged from the 59 suggestions made in respect of research priorities for CYP; these were then additionally grouped into six “areas”. Those areas (shown in Fig. 1a) were as follows:

1. “Body Systems”, including: cardiovascular (1); breathing (1); exercise (2); growth (1); teeth (3)
2. “Lifestyle and lifespan” including: general health (2); daily activities/autonomy (5); fatigue (1); emotional wellbeing (1); mobility (5); pregnancy (1).
3. “Interventions” including: physiotherapy (4); OI prevention (2); medicines (10); gene therapy, transplantation (6).
4. “Bone specific” including: Bone healing (4); deformity correction (4); comfort plaster (1).
5. “Testing/clinical assessment”: DNA testing (3).
6. “Other research”: Basic research (2).

A single suggestion - “magic” - was excluded from consideration and an additional suggestion to improve education for medical professionals regarding OI was not included.

The willingness of children to undertake specific interventions is shown in Fig. 1b, and their willingness to participate in different study types in Fig. 1c.

Forty-one different themes emerged from the 167 suggestions made in respect of research priorities for adults; as for CYP these were grouped into the same six areas (see Fig. 2a) as follows:

1. “Body systems”, including muscle (1); teeth (7); growth/weight/obesity (3); breathing (3); gastrointestinal (3); hearing (3); vision (1); cardiovascular (4); fatigue/endurance (3); effect of menopause (1); sleep (1); hypermobility (1).
2. “Lifestyle and lifespan” including: healthier lifestyles/lifespan (6); emotional wellbeing/psychological aspects (8); mobility including vehicles, robots (3); activities of daily living, accessibility and autonomy (12); nutrition and supplements (6); pregnancy/fertility (4); mental health (1); talent development (1); exercise (4); work (3).
3. “Interventions” including: medicines including adverse effects, bone strengthening treatments (19); gene therapy, bone marrow transplantation (3); physiotherapy and rehabilitation (7); OI prevention (7); pain relief (3); alternative therapies (3); joint prostheses (1).
4. “Bone specific” including: spine (2); correction of malformation/rodding (5); fracture risk determinants (1); Preventative or acute treatment for fractures (3); callus formation and bone healing (8).
5. “Testing/clinical assessment” including: bone density assessment (5); heredity (4); DNA testing/diagnosis (9); phenotype determination (2).
6. “Other” research including: Basic science research (3); health services research (5).

The willingness of adults to undertake specific interventions are shown in Fig. 2b, and their willingness to participate in different study types in Fig. 2c.

For both adults and CYP, medicine/advanced therapeutics or interventions to strengthen bone were the single most common suggestion.

Both adults and CYP appear generally more supportive of undertaking activities that support their priorities, with the only test receiving less than 60% support overall being the skin biopsy.

The comparison of the results in terms of research priorities across the six areas is shown in Fig. 3a for CYP and adults separately as bar charts of the percentages of the total. Overall, the results were quite similar; CYP appeared to be more focused on interventions generally, whereas adults were perhaps more concerned with prioritisation of research that could enhance lifestyle and lifespan.

Finally, in terms of participating in interventional studies there appeared to be a higher level of willingness to participate in studies amongst CYP as opposed to adults – 51% vs 24% - generally, although very few children and no adults were willing to consider participating in studies of new surgical procedures (Fig. 3b). For CYP, the factors influencing their decision to participate or not included their trust of the person asking the question; support from their patient group or association; the risk and discomfort compared to the perceived benefit; and the need for anonymity. For adults, the determining factors were the desire to be treated as a collaborator and expert patient; altruism; and the personal cost in terms of time and money.

Discussion

In this study we found that both children and adults with OI were interested in research that improved outcomes that were meaningful to them, particularly in the areas of bone-directed therapeutics and quality of life including activities of daily living, mobility, relief of pain and improvement in the feeling of fatigue. Both adults and children with OI fracture far more frequently than does the general population, with children in turn fracturing more often than adults. (16) Fracture is a major influence in the lives of individuals with OI, not just in terms of the acute effects of pain and reduced mobility, but also in terms of impacting school attendance for CYP, and access to work for adults. Fracture also may lead to deformity and the need for corrective surgery with all its attendant risks.

Fracture risk reduction is the focus of regulators' attention when deciding on the design and conduct of studies in this area; nevertheless, the data we have gathered clearly show that quality of life, including pain, fatigue, and mobility are important priorities from a patient perspective in OI. Study designs should pay attention to these issues and collect relevant data that will enable those commissioning healthcare to be assured that the proposed intervention, whatever it might be, meets the needs that patients perceive they have.

The participants' willingness to undergo assessments of various degrees of invasiveness was similar between adults and children, but adults seemed less willing overall to participate in interventional studies. It would be important for investigators contemplating studies in future to be aware of the possible difference in attitude of children as opposed to adults in considering participation in research, as well as the factors identified as being important in determining participation. It is clear also that those with OI would prefer to be offered something rather than nothing – hence the lower willingness to participate in placebo-controlled trials.

The involvement of patients and carers in establishing research priorities has become an established part of developing a more targeted approach to research in recent years. A number of organisations, notably the James Lind Alliance (JLA) with their Priority Setting Partnerships (https://www.jla.nihr.ac.uk/priority-setting-partnerships/) in the United Kingdom and the Patient Listening Sessions (https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-sessions) set up by the Food and Drug Administration in the USA, have developed extensive portfolios of work in this area. In Europe, EURORDIS (https://www.eurordis.org/) acts to "empower, partner and advocate for people living with a rare disease"

Our experience of seeking the input and advice of parents and children with OI began at a UK Brittle Bone Society annual conference for children, adults and families. We undertook a survey of conference participants using post-it notes and flipcharts. We noticed that what children as opposed to their parents said they wanted were not always the same and we developed the methodology for this study specifically to be able to distinguish the adult and child voices. We also chose to undertake the work as a face-to-face exercise with small groups, recognising that that might lead to some bias, but also hoping that the more interpersonal setting would encourage the children particularly to engage with the study. This is in contrast to the more questionnaire-based and "remote" approach of the JLA.

We did not aim to develop a "top ten" set of specific priorities at this stage. We were more interested in comparing and contrasting the different views of children and adults, in ascertaining to what extent and why they would be prepared to participate in research, and from a practical standpoint, what sort of research procedures would be acceptable to them.

The findings were not surprising in terms of the overall priority areas, and also aligned with our direct clinical experience of the willingness of individuals to undergo a range of more or less invasive tests. The factors influencing likelihood of participation were also ones that we largely expected. The finding that adults in particular wish to be seen as collaborators and "co-producers" in managing their own health is one that has been evident for some time in many areas,(17) but clearly reinforced here in relation to conducting research. The need for anonymity in respect of the children may to some extent reflect the age of the child participants, who were essentially adolescents.

We recognise that there are likely to be biases in the collection of the data, reflecting in part the geographical spread, access to health care and expert professional input in different parts of the world.

There will also have been biases in relation to the self-selection of focus group participants, as well as their ability to attend face-to-face sessions despite the provision of some support to do so.

Conclusion

Both adults and children with osteogenesis imperfecta are willing to undergo a range of more or less invasive tests and assessments to pursue their stated research priorities. They are keen to be co-producers rather than patients in this context. Children seem more willing than adults to participate in interventional studies. For both adults and children, their ability to participate in interventional studies in terms of the personal cost to them - time, money and impact on work or school - should always be considered and mitigated.

Declarations

Ethics approval and consent to participate

Approval from relevant ethics committees was obtained in each participating country. The study was approved in the UK by the Health Research Authority IRAS project ID: 262258; protocol no. SCH-2369; REC reference 19/LO/1249. All participants signed informed consent forms having read the relevant participant information sheets; those under the age of consent signed assent forms and consent forms were signed by their parents or guardians.

Consent for publications

Not applicable.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests.

The authors declare that they have no competing interests.

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Authors’ contributions

CH and NB designed the study and obtained the funding. CH, EY, EM, AR, VP-B, AM, CV and DG organised and ran the focus groups, transcribed and cleaned the focus group outputs and read, amended and approved the manuscript. CH and NB collated and interpreted the data and wrote the original manuscript. All the authors have seen and approved the submission and agree to be personally accountable for their contributions.

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Not applicable

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Figures

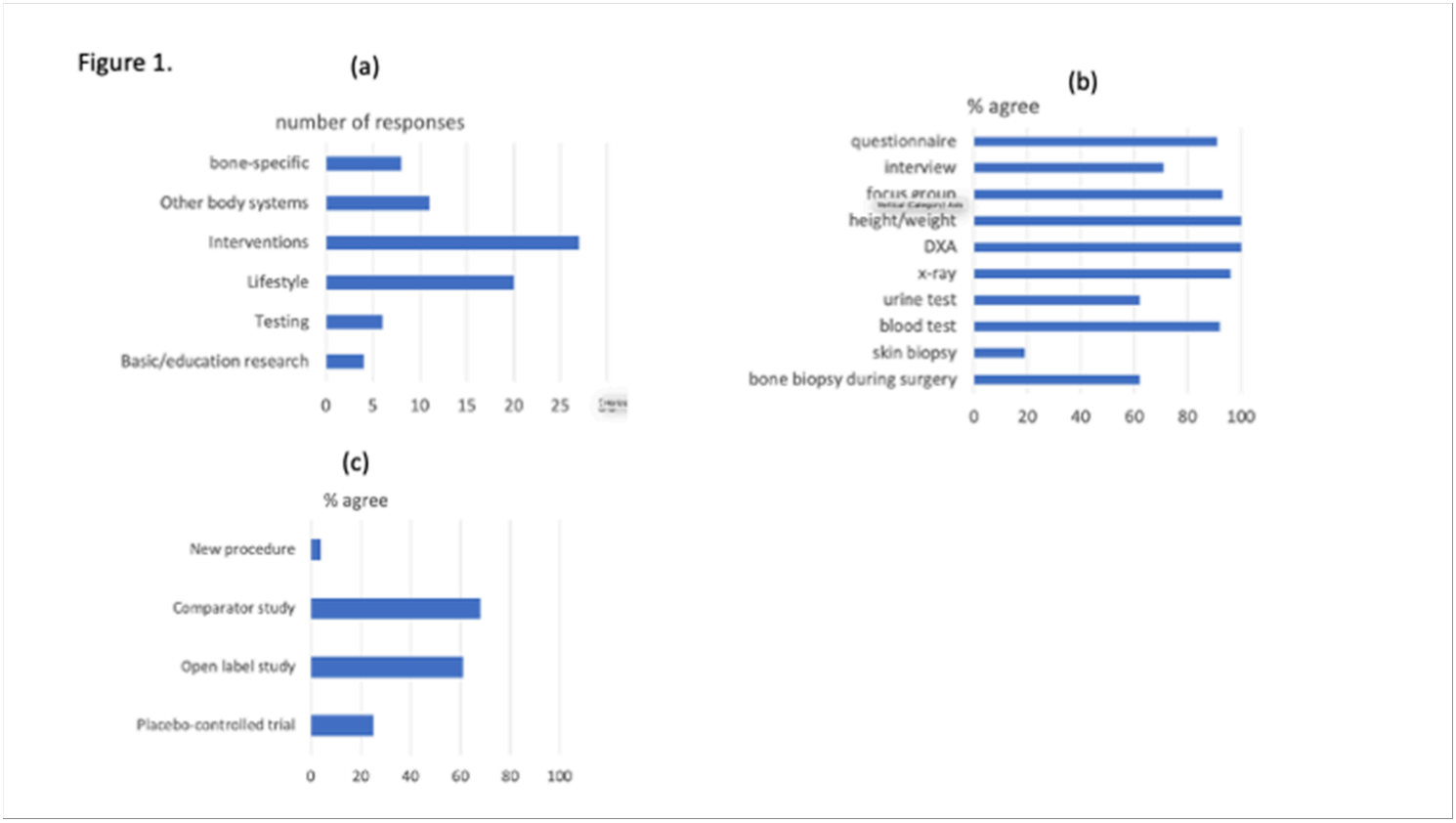


Figure 1

a. CYP's research priorities

b. Acceptability of assessments in CYP

c. Which interventions do CYP prefer?

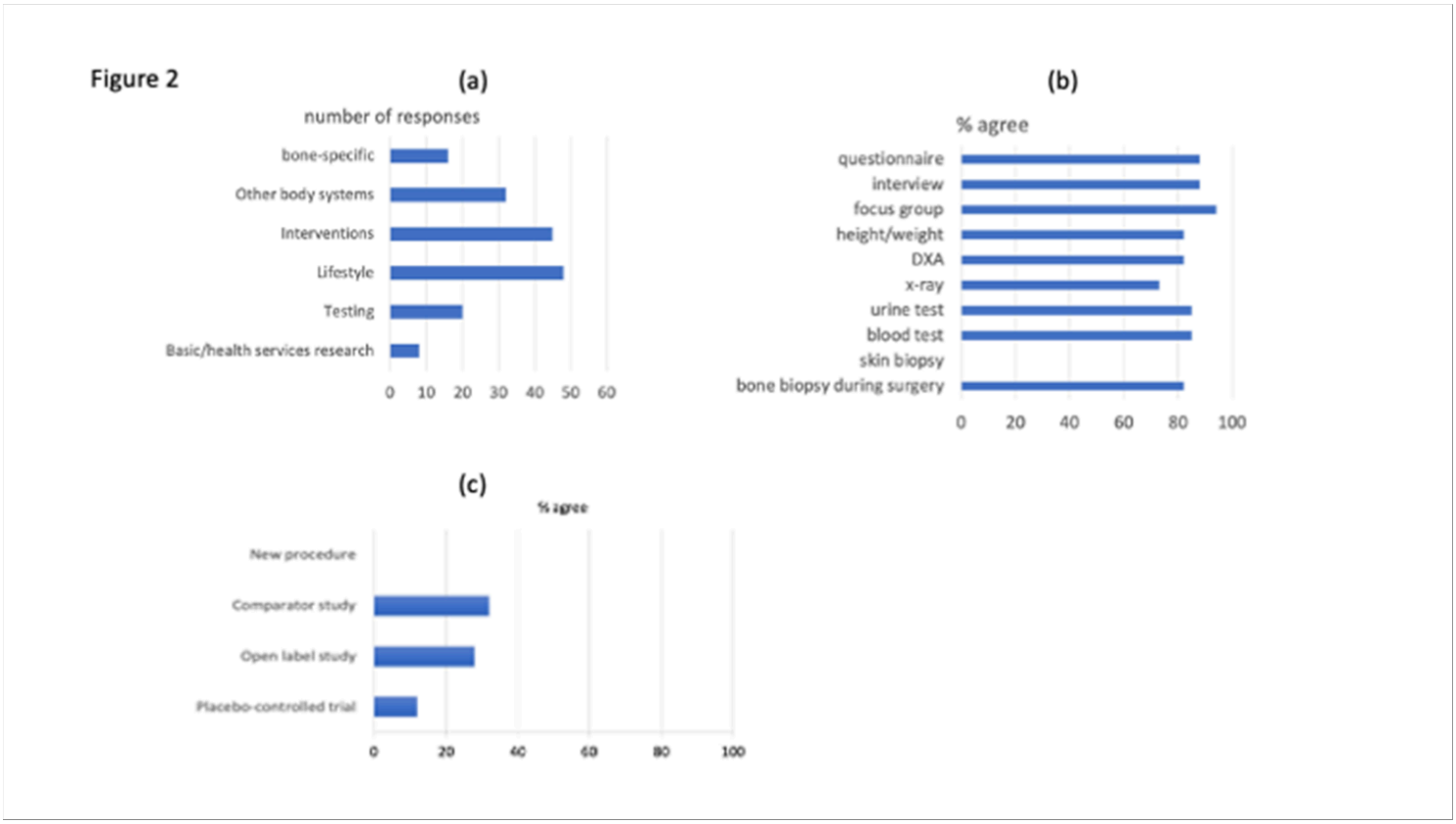


Figure 2

a. Adults' research priorities

b. Acceptability of assessments in adults

c. Which interventions do adults prefer?

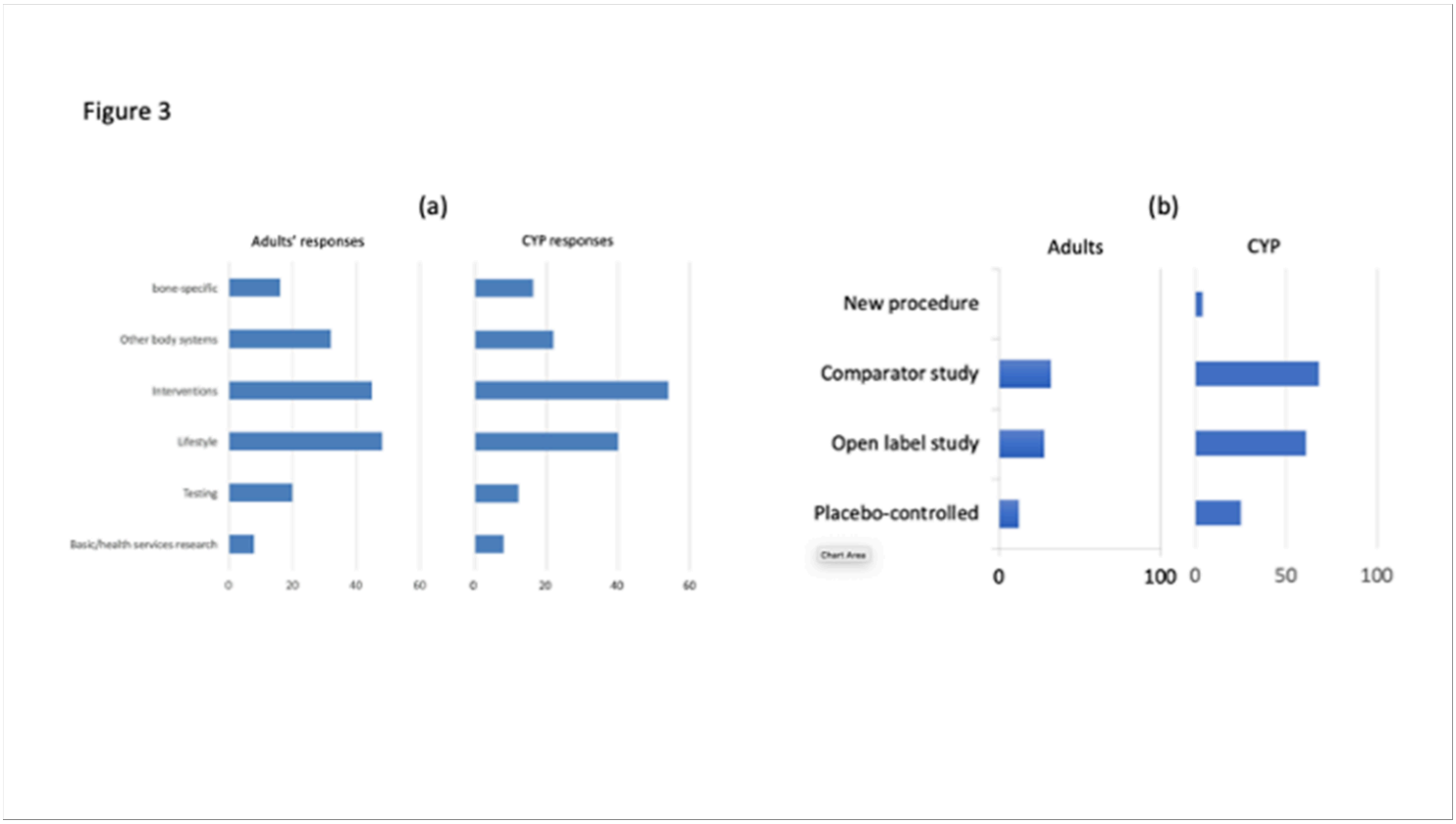


Figure 3

a. Adult vs CYP priorities

b. Comparison of preferred interventions between CYP and adults