Comments from a contributor wishing to remain anonymous

Response to EU Consultation
Ethical considerations for clinical trials on medicinal products conducted with minors

Introduction

Dear Committee
Thank you for the opportunity to comment on this ethical considerations document. By way of introduction I have

- conducted hospital and community paediatric clinical trials for 17 years
- been a member of the FP7 and ERC ethics panels since 2008 (my views here are independent)
- advised industry on the practical & ethical issues of paediatric clinical trials since 2004
- written lay language information sheets for parents and children since 1999
- given paediatric ethics training at conferences and 2 universities (UK and CH)

I don't have formal ethics qualifications but have spent many years working with families and children, and submitting and reviewing ethics applications. I hope my comments will be of use but please feel free to get in touch if there are further questions or I have misunderstood anything.

Kind regards and best wishes

General comments

- **Partnership model**: There is a myth circulating that ethics are a barrier to research. Conversely Good Ethical Practice is a partnership that seeks to obtain a win-win for science and society. I trust that by making your excellent ethics document a more user-friendly guide (see below), it will help the ethics community, researchers, regulators, investigators, the public and families alike collaborate in bringing safer and more effective medicines to children.
- **Minimising risk and distress:** Suggest that the focus is not just on *assessing* the risk and burden, but researchers need to clearly demonstrate in the protocol and to the ethics committee how these risks will be *prevented or ameliorated*. Low risk procedures may be distressing. Unfortunately the sicker the child, the more invasive the procedure in order to help that child. Therefore the justification for each procedure is essential. Every effort must be made to minimise both risk and distress to the child and his/her family. To cite **Flynn 2003** "it is incumbent on researchers to develop research procedures that will not only answer the scientific questions of interest but also protect this vulnerable patient population from harm". (1)
- Concrete examples are helpful. E.g. *"To minimise risk and distress of the blood test, local anaesthetic cream will be offered. Only staff trained and experienced in venepuncture will be permitted to do this. A second attempt is only allowed with the express permission from the minor and their parents, and only if the child and family are not distressed*"
- **Definitions**: Unfortunately the document has confused consent with assent in several places
- **Readability of ethics document**: As we are advocating information to be easy to read it would be helpful if this document is likewise clearer. Use of shorter paragraphs and bullet points etc. It would also help to provide a brochure format to make a difficult subject easier to digest. A good example is the **Social Research Association** Ethical Guidelines on-line PDF (2)
- **Teenage parent**: What do you want us to do if the parent is also below the age of majority for

consent? Should both sets of the child's grandparents sign consent? Local ethics decision?

- **Agreement:** Could "Agreement" be called "Voluntary agreement" as children may agree out of a sense of duty or social desirability to please parents/doctor/altruism etc.
- **End of life & genetic testing**: A section on these areas would be helpful
- **Member State authority ethics contact:** It would be helpful for this document to include a contact organisation and contact details for up-to-date information regarding age of consent and assent for that country.
- **Weight**: this is a practical problem that is also a **safety** issue and we are mandated to do no harm. There is no standardization of how children are weighed for pharmaceutical research. This is critical as drug dosing as you know is usually weight or surface area based. Suggest that children should always be weighed on recently calibrated scales in underwear without shoes to avoid seasonal variation of light or heavy clothing. Should children with heart failure be weighed before or after diuretics? We are never told and it may vary from site to site.
- **Public perception of testing medicines with children:** Many parents do not realise that medicines prescribed for their children may not have been tested on children and can cause harm if best dose not known etc. Suggest it is an ethical imperative to educate the public about clinical trials with children in order to gain their trust and improve recruitment and compliance. Perhaps this could be explored and ameliorated using a Horizon 2020 or European Research Council collaborative grant if this has not been done already?
- Suggested text in blue

Line	Text	Comment/suggested text
27	Regulation to respect the explicit wish of a minor to refuse participation in, or to withdraw from, a clinical trial at any time;	• Suggest you need a clear definition of **dissent** and how this will work in practice (e.g. **Wendler 2006** stop assess address communication strategy during procedures to ensure child can stop anytime if distressed) [3]
29	Recommendations on the requirement of participation of the minor in the informed consent process;	• Definition of minor can vary from country to country • Suggest you define minor for purposes of this document • Suggest caution – minors participate in the ASSENT process. Consent is for the parents or legal guardians on the child's behalf
31	Introduction of the term 'agreement', equivalent to the term 'assent' in medical 31 literature, since the Regulation reserves the term 'assent' to have legal value in some 32 Member States;	• **Voluntary** agreement • Suggest this statement is confusing as there are differing definitions of assent in the literature. In the US, assent can mean a degree of cognition around the decision, in the EU and elsewhere it is linked to the child being below the legal age to consent to research. • True assent or consent is <u>never possible</u> for a child or adolescent. The brain's frontal cortex - where cause and effect, risk and benefit, decision making processes occur - do not finish

		myelinisation and maturity until the early twenties. • Extreme caution is therefore required where the **parents** of study children are **adolescents.**
34	More emphasis on informed consent as a continual process;	More emphasis on informed consent **and assent** as a continual process **before and during the study** ;
35	More emphasis on burden, next to risk, its subjective nature and the importance to involve children in the assessment and minimisation of burden;	• Do you mean involvement of children in preparation of protocols? • Minimisation of burden essential if paediatric trial to be "doable" but this sentence sounds as if children are being involved in the minimisation. Please clarify
69	6.2 PARTICIPATION OF THE CHILD IN THE INFORMED CONSENT PROCESS	• 6.2 PARTICIPATION OF THE CHILD IN THE INFORMED ~~CONSENT~~ **ASSENT** PROCESS
72	6.5 WITHDRAWAL OF THE CONSENT	• 6.5 WITHDRAWAL OF ~~THE~~ CONSENT **AND ASSENT**
73	CONSENT, ASSENT AND AGREEMENT IN EMERGENCY SITUATIONS	• CONSENT, ASSENT. **DISSENT** AND **VOLUNTARY** AGREEMENT IN EMERGENCY SITUATIONS
81	*7.2.4 Adolescents (10-18 years of age)*	• Suggest you add a section here for 16-17 year olds. In some Member States, the age of consent to research is 16years. This in-between age group will need easier information materials than for the parent/legal guardians.
84	8. EXPERTISE REQUIRED FOR ASSESSMENT	• Suggest adding **Patient groups, families and older children**
146	The document provides recommendations on various ethical aspects of clinical trials performed in minors from birth up to the legal age of competence to provide informed consent.	• Suggest this is unhelpful as legal age of competence a) is not homogenous to all countries b) children who are legally able to consent to research for themselves still need legal and ethical protection. Suggest • …..from birth **to 18 years**. ~~the legal age of competence to provide informed consent.~~
152	As the authorisation of clinical trials, including ethical approval, is performed by the Member States, any recommendations on ethical aspects of clinical trials in minors will also facilitate a 153 harmonised approach to the application of the clinical trials Regulation across the EU, thereby 154 facilitating the conduct of clinical trials across the EU, in whichever country the clinical trial 155 in minors occurs.	• Have you checked the legal basis for this? • What exactly do you mean by harmonisation as this is a technical term relating to ICH and could cause confusion Will recommendations facilitate harmonisation if you say at the beginning • *"This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area"*? • Suggest that a harmonised approach can be strived for but cannot be mandated as ethical approvals are designated to the

		countries where research takes place
162	The difference between minors and adults as research 162 participants has implications on the design, conduct and analysis of trials, which should also include paediatric expertise.	• Grammar: Do you mean **Paediatric expertise is essential for the design, conduct and analysis of paediatric trials due to the many differences between minors and adults as research participants and patients**.
164	Pain, fear, discomfort and parental separation should be prevented and minimised when unavoidable.	Pain, fear, discomfort ~~and parental separation should~~ **must** be prevented. Parental separation **– especially during procedures must be minimised wherever possible** ~~when unavoidable.~~
170	Off label use of medicinal products in children without proper evidence poses an ethical problem	Off label use of medicinal products in children without proper evidence poses an ethical problem **due to the increased and actual risks of morbidity and sometimes death of child patients.**
199	However, a 'staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended	Delays in data availability should be balanced against the need to protect very young children from harm.
257-263	The Regulation requires their full engagement with the aim to treat children as developing autonomous beings	Excellent. Perhaps add The Regulation requires their full engagement with the aim **wherever possible** to treat children as developing autonomous beings **during the planning and implementation of the research.**
339	**5.2 Assent** In this document, "assent" should be understood as a legally required expression of the 339 minor's will to participate in a clinical trial, dependent on Member State law.	In this document, "assent" should be understood as a legally required expression of the minor's will to **voluntarily** participate in a clinical trial. The **age of consent to research** is dependent on Member State law.
343	The minor's assent is not sufficient to allow participation in 343 research unless supplemented by informed consent of the parents/legally designated 344 representative. 345	The minor's assent is not sufficient to allow participation in research unless supplemented by **written** informed consent of the parents/legally designated representative.
352	It means the expression of the minor's will to participate in a clinical trial	It means the **voluntary** expression of the minor's will to participate in a clinical trial
360	Lack of agreement does not necessarily mean the child will not participate, since it may be evaluated that the child is not mature enough to express agreement.	Possibly if child very small. However suggest adding **However if a child is persistently and inconsolably distressed by a research-only procedure (e.g. venepuncture) the procedure must be stopped immediately and the child withdrawn from the study**
381	When the term "children" is used within these recommendations, it is used consistently with 3the provisions of the Clinical Trials Regulation to mean minors, in contrast to ICH E11 383 guideline which refers to children as individuals aged from 2 to 11	• This is very confusing as you do not appear to have clearly defined who a minor is • It is worth explaining in the document that e.g. in some MS the age of legal majority is 18 years but "minors" can sign **consent** to

	years.	research aged 16.
417	Article 2(2.18) of the Clinical Trials Regulation:	Reference is Article 2 (18)
438	The information should be given to each parent, or the legally designated representative, both in oral and written form. Article 29.2(a) describes the information that should be provided.	Suggest include **2 (b**) here as well, which states that the information shall **"be kept comprehensive, concise, clear, relevant, and understandable"** otherwise consent will not be informed.
463	If an adolescent is no longer a minor as defined by the Clinical Trials Regulation, or is an "emancipated minor"[5], then written informed consent is required from these individuals as for 464 any adult capable of giving consent.	Note that these participants will need a consent form that is not just cut and pasted from the parent version but needs to be written in simpler language while still retaining the meaning
477	***6.2 Participation of the child in the informed consent process***	• Do you mean child or minor here? Children are involved in the **assent** process not the consent process unless they have reached the age of majority in their country to consent to research • ***6.2 Participation of the child in the informed ~~consent~~ assent process***
482	Where appropriate, a translator and/or a cultural mediator, familiar with medical terminology, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available in the process of obtaining informed consent	This is very difficult: • It is too late to have someone with all these requirements at the time of informed consent. Suggest "Where appropriate … and particular ethnic differences should be available in the **planning of the study and during the** local **process** of obtaining informed consent **and assent** • Some countries will have a large migrant population so sponsors must also translate information and do a back translation to ensure local comprehension • **Adverse event reporting** Very important to ensure that the family who cannot speak the language has someone easily accessible with good communication skills available to report and record AEs in a timely manner – especially if the child is very ill.
491	**Continuous consent/assent** and that might affect the willingness of the parents and child to continue.	……that might affect the willingness of the parents and child to continue **or require written re-consent /assent with a revised information sheet and consent form**
530	It must be emphasised that after a child withdraws from a trial, the investigator is still responsible for reporting trial-related events. In addition, the investigator needs to assure appropriate treatment and follow-up.	• Documentation to the sponsor may not be possible legally as once consent is withdrawn, this may also include post withdrawal data unless clearly stated on the informed consent documentation and agreed in advance.
565	***Consent, assent and agreement in emergency situations***	A few ideas – thinking aloud • Keep bosses of central and local **ambulance crews** informed and thanked – as they

		could perhaps be designated to take preliminary consent and assent in the ambulance on the way to hospital if time? • Consider verbal consent from parent/legal guardian to be recorded over phone e.g. if child taken ill at school • One could explore the idea of identifying children who have assented/consented with their parents in advance, by using a discrete temporary tattoo? Can be removed with baby oil but not recommended for children aged 5 or under. Wrist bands were tried once in an epilepsy study but these were swapped with friends! • With Ethics committee permission, consider advance notification using radio advertising or discussion about the study to raise local awareness
651	It is recognised that children from the age of 3-4 years can express altruism and have an emerging capacity to form an opinion.	• Investigators should proceed with caution where children participate to help other children. I have seen children very upset when assented to take part but screening found the research to be unsuitable for them
666	The dissent should be respected, as these children are capable of forming an opinion of their own.	• Dissent should be respected whatever the age of the child
673	*7.2.4 Adolescents (10-18 years of age)*	• Assent for pregnancy testing may need to be performed separately where the girl starts menarche aged 8 • Adolescents may be parents in their own right • Older adolescents may prefer to consent/assent at a non-paediatric clinic
699	***7.3 Difference of opinion between the child and the parents/legally designated representative***	• In rare cases a dissenting child has been entered into a trial against their will if their disease is life threatening and the e.g. cancer drug is their only hope of survival. Should be considered on a case by case basis and referred to the clinical ethics committee/a Judge if necessary
736	In paediatric trials minimising the number of subjects and the level of risk and burden is especially important. This may require smart trial designs,	• … smart trial designs **e.g. use of Bayesian statistics**
748	The protocol should justify the duration of follow up in the given paediatric population. Follow up must include assessment of physical development (e.g. Tanner staging) where appropriate.	• Tanner staging likely to reduce recruitment to zero as is personally invasive and very sensitive for adolescents. • Suggest only request where absolutely

		necessary e.g. endocrine disease • Could have Tanner score as optional unless main endpoint of study? • Suggest modified Tanner methodology. During the physical exam the doctor makes a mental note of the child's stage of puberty. There is no need to touch or measure the child's genitals but stage can be compared against a visual scale after child has left the room.
800	To ensure feasibility of trials to be performed, the investigator and protocol writer should 800 ensure that there is involvement of children (suffering from the relevant condition) and of 801 families in the development of information material, and where feasible also in the design, 802 analysis and conduct of the trial.	• To ensure feasibility of trials to be performed, the investigator and protocol writer should ensure that there is involvement of children (suffering from the relevant condition), **patient organisations** and of families in the development of information material, and where feasible also in the design, analysis and conduct of the trial.
804	The trial should be designed to minimise risk and burden for subjects.	• Please do not call them subjects, they are people! • Risk can also include psychological risk e.g. **Needle phobia** should always be an exclusion criteria but I have never seen this in protocols The trial should be designed to minimise risk and burden for ~~subjects.~~ **participants and their families by e.g. reducing number of blood tests, scheduling visits at convenient times.**
842	Instruments to 842 document PROs and health-related quality of life in children are increasingly available.	• Suggest caution to ensure identity of person inputting data e.g. PIN code etc
849	In addition, ….. and require often more trial sites.	Grammar: and **often** require ~~often~~ more trial sites.
861	Long-term use (beyond 3-6 months) of placebo is known to create difficulties in acceptance 861 of the trial by participants and to increase drop-out rates.	Long-term use (beyond 3-6 months) of placebo is known to create difficulties in acceptance and **compliance with** the trial by **parents** and participants, and **also increases** drop-out rates.
895	Reference?	Is missing or perhaps typo?
904	*9.2.4 Clinical trials using medicinal products containing radio-isotopes*	Remember to test for pregnancy if using radio isotopes.
906	**10. The concept of benefit**	Study children also benefit educationally by learning more about their bodies and how to control their disease e.g. asthma, cystic fibrosis, diabetes
933	Furthermore, at the start of a randomised controlled trial, all participants have an equal chance to be allocated to either arm.	Suggest this is not always possible as randomisation may also be to different doses of same or comparator drug, or not be 50:50

		treatment-placebo for **safety** reasons. However suggest the principle of justice as defined in the **Belmont report** applies to ensure a fair distribution of risk and benefit in research.[4]
959	***10.3 Classification of trial protocols***	• Benefit to study population also affected by availability of licensed medicine in country where study performed • Consider compassionate use
1035	***11.2 Assessment of burden***	• Please use shorter paragraphs to ensure this excellent section is read
1123	Stopping rules should be included in the protocol,	• Especially important is the **number of venepuncture attempts** allowed for a research-only sample. Second attempt should only be permitted with explicit assent from the child and as long as he/she is not distressed.
1153	…..direct benefit for the minor, there is a realistic possibility that their health or wellbeing will be improved by participating in the trial,……..	**……..However this should not be used as an inducement to participate or raise false hope.**
1207	**Subsidiarity**	• Could you use a different word for this as it is confusing as also relates to EU law? • Please clarity
1260	For instance, when the minor no longer has a prospect for cure, standard treatment is palliative care.	• Very difficult ethical issues here and beyond my ability to comment. Suggest obtaining advice from palliative care teams. • A section regarding research with these children would be of great value here. • Caution regarding consent/assent to avoid conflicts between altruism, acceptance of increased risk and wish to please doctor.
1312	Blood samples: Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks	• Is this evidence based? • Also consider the amount of blood taken for clinical purposes in the preceding month, and what the Hb/serum ferritin status was to ensure very small children are not over tested.
1353	**Trials with adolescent females**	• Pregnancy testing must be performed at least monthly. Hcg should be done prior to study drug being taken and monthly urine tests may be acceptable • Remember urine less reliable than blood tests (yes - brother's urine has been used). Dilute urine of many teenagers drinking lots of water can result in a false negative reading. However this needs to be balanced against increased number of blood tests unless these are required for clinical reasons. • Ethics committee and parent acceptability of pregnancy tests and contraception may vary between Member States • Does the drug also affect **sperm** and will you

		require **boys** to wear condoms? • There must be a **positive pregnancy plan** in the risk management plan for the study. • **Contraception and protecting the foetus from harm**: Clearly there is a need to protect the foetus from harm of study drug but it could be argued that some protocols appear to be encouraging under-age sex. Companies should **not** cut and paste requirements for adult birth control into paediatric protocols but ask for local ethics/IRB/country advice. • Will you require testing for recreational drugs? They are taken on a regular basis by many adolescents and cause risk of interaction with study drug
1451	Parents/legally designated representative can only be compensated for expenses and loss of earnings directly related to participation in the clinical trial.	• Area for confusion and debate: Will sponsors be required to pay a mother who is a lawyer for a day's pay lost by taking her child into a study? How will this be managed equitably as parents have different rates of pay and those who are not employed still have to give up their time to help with the research? • **Teenage participants** may be employed. • Suggest payment of sibling childcare expenses to facilitate study visit.
1453	**22. Insurance issues**	• Caution here as hospitals may have insurance to cover paediatric trials, but universities may not, or only provide partial cover
1508	Public information with warnings on the unethical aspects also contributes to education on how to conduct paediatric trials ethically	• What do you mean by public information? • Please clarify – do you mean there should be an ethics section in the paediatric trial lay summary? Thanks
P40	Annex 2: Information The number of age-specific variations of sets of information material should be kept to a minimum number required to include substantially different wording or presentation.	• Unfortunately this is not possible as there is a legal requirement under the Clinical Trials Regulation Art 29 2(b) which states information is "kept comprehensive, concise, clear, relevant, and **understandable to a layperson**". E.g. due to the wide **reading age** of children between 12-18 years, it is imperative that two or more versions are used. Especially if consent information is needed for 16-17 year olds.
P40	**List of items recommended to be covered in the information sheets:**	**List of items recommended to be covered in the information sheets as applicable. These should be in lay language** This list appears to be from the UK Health Research Agency website. The list is not a one size fits all – but rather these are questions to be used as appropriate • Ask "Why are pregnancy tests needed for girls taking part? • Some questions could be combined, depending on the age group

	What will I have to do? What will my parents have to do?	Please delete this question – the research is **voluntary** and they do not have to do it! **What will we be asked to do if we agree to take part?**

P43	**Table of procedure risks – suggestions as requested**	
	Category ONE – low risk	
	Move items?	**Why**
	Tanner staging to CAT 3	It is of low physical risk but is extremely personally invasive and there is the risk that children will refuse participation and so a good drug may not get to market.
	Behavioural & psychological testing to CAT 2	Again this is very private information and there is a risk of the child feeling stigmatised which could be actual or perceived
	All needle related items move to CAT 2	• s/c cannot be described as low risk as it depends what drug is being given • (Needle phobia **must** be an exclusion criteria) • Venepuncture and finger pricks with children can cause severe distress and affect the efficacy of future hospitalisations or treatment • Heel prick – there is risk of damage to calcaneus & subsequent infection. Should only be performed by those with expertise
	Collection of sputum to CAT 2	• Ordinary coughing up of sputum is low risk, but if this is a formal asthma test involving inhalation of salty steam, this is very unpleasant
	Lung function tests listed could remain in CAT 1	• Non-invasive and low risk, however if child has serious respiratory disease repeated manoeuvres can be very tiring.
	Oral GTT move to CAT 2	• Involves venepuncture and fasting
	Ophthalmoscopy – 1. Ordinary eye exam can stay in CAT 1 2. Eye exam using **drops to dilate pupil** move to CAT 3	1. No risk as long as equipment and procedure explained well 2. High risk of distress - The drops to dilate the pupil **STING** momentarily and usually results in a little child screaming with pain.

P43	**Category TWO – procedures performed routinely but not without risk**	
	Move items?	**Why**
	Urine collection via endo-luminal or suprapubic catheter – move to CAT 3	• I am not sure - but theoretical risk of infection, perforating other organs if baby moves? Suggest this is not justified unless also needed for clinical reasons.

	Transcutaneous oxygen or carbon dioxide tension monitoring – move to CAT 3 for babies and neonates	• Avoid prolonged monitoring for research purposes and ensure local protocols complied with. Probe can damage skin if left on for too long
	Umbilical catheter move to CAT 3	• Very distressing for baby, very invasive can introduce infection. Suggest the use of UAC only justified if needed for clinical reasons anyway or if this is only method of delivering drug for emergency trial?
	Exercise testing could stay at CAT 2 but move to CAT 3 if serious disease	Especially relevant for heart lung disease
	Fasting (≥ 1 meal) – suggest this is not an appropriate description as fasts are usually in terms of hours. 1. If fast overnight for older child stay CAT 2 2. Babies move to CAT 3 Need strong justification for fasting as children find this distressing	1. e.g. School age children (say 6+ years) can usually manage fasting overnight for surgery 2. Get local guidance. Little babies normally cannot go without milk for 4 hours. Timing of fast is essential and must be age related.
	Spinal CSF tap move to CAT 3	• Need strong justification if CSF required for research purposes alone as very invasive and risk of injury if child won't stay still. Child will need sedation which has risks. • Better justified if spinal tap being done anyway and a small amount of extra fluid required for research purposes as long as within local clinical guidelines for age of child
	Bone marrow aspiration – move to CAT 3	• Need strong justification if bone marrow required for research purposes alone as very invasive and painful. Child will need sedation or general anaesthetic which has serious risks. • Better justified if aspiration being done anyway (e.g. for diagnosis of Acute Lymphoblastic Leukaemia) and a small amount of extra marrow required for research purposes.
	MRI scan routine – move to CAT 1 MRI scan with contrast – move to CAT 3 MRI scan with sedation – move to CAT 3	• Procedure low risk but child will need explanation and reassurance regarding e.g. parental separation, loud noise and small space. • Requires venepuncture and contrast could cause allergic reaction • All procedures requiring sedation can be high risk, especially if child vomits whilst in MRI machine – risk of aspiration even if closely supervised from next room • fMRI has issues around privacy
	CT scan routine - stay at CAT 2	• Low risk if not sedated, child older and **not pregnant**

	CT scan with contrast – move to CAT 3 CT scan with sedation – move to CAT 3	• Requires venepuncture and contrast could cause allergic reaction • All procedures requiring sedation can be high risk,
	Paracentesis – move to CAT 3	• I am surprised this a research procedure as it is usually done for clinical reasons • Very invasive. May require sedation and has numerous serious risks e.g. of infection. shock due to drop in blood pressure, perforation of bowel or other organs, haematoma, leak from injection site etc
	Skin punch biopsy move to CAT 3	• Painful, infection risk, may require sedation
	Airways or skin hyper-reactivity challenge test Move to CAT 3	• Risk of severe allergic reaction, asthma attack and can be very distressing

P43	**Category THREE – high risk**	
	Move items?	**Add items?**
	All procedures listed here are high risk so remain in CAT 3	• Suggest adding **endoscopy, bronchoscopy** and **colonoscopy** as procedures very invasive and require sedation. Endoscopy and bronchoscopy can cause aspiration of wobbly teeth into lung therefore ensure prior dental checks etc

	References
	1. Flynn J T **Ethics of Placebo Use in Pediatric Clinical Trials The Case of Antihypertensive Drug Studies** Hypertension. 2003; 42: 865-869 2. Social Research Association **Ethical Guidelines** 2003 http://the-sra.org.uk/wp-content/uploads/ethics03.pdf 3. Wendler D S **Assent in paediatric research: theoretical and practical considerations** J Med Ethics 2006;**32**:229-234 4. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research **Belmont Report** (1978)