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Ethical issues of clinical trials in paediatric oncology: A systematic review over 10 year developments (2003-2013).

Background

Even the utmost technically sound decision must be grounded on firm ethical reasons. Throughout the cancer journey, patients, parents and health professionals need the peace of mind that comes with the conviction of acting in the right way.¹ Instead, there is a risk for conflicts, reckless decisions and diminished self-image. Accordingly, professionals, parents and patients have to act in a transparent, deliberate and concerted way, which involves to establish amongst them relations based on “alliance” (trust) and “deliberation” (justification).

In paediatrics, this also requires to tailor our attitudes to each patient’s age and maturity, for acting appropriately has both moral and educational dimensions. Especially, to carefully seek minor patients’ assent in healthcare or research environments is both a matter of showing respect for their evolving autonomy, as well as a way to address their need to exercise agency.²

Coordination and like-mindedness are even more important in research settings, where participation in a clinical trial has to follow a true decision of deviating from standard healthcare pathways.

Despite off-label drug use (in absence of paediatric development) and high levels of research participation in paediatric oncology, there is still a clear distinction to be drawn between care and research. Indeed, while prospects of individual benefit are perfectly known in standard care, these are ranging from unpredictable (ph. 1) to uncertain (ph. 3) in clinical research. It is all the more challenging for families to make a decision that, while prospects of benefits are unknown, exposure to risks of toxicities remains certain (though minimised).

However, as shown by a recent review, compliance with biomedical ethics principles is often insufficiently documented in scientific publications.³ Lack of proper documentation does not necessarily mean that ethical standards are not met, nor underestimated by investigators; lack of clarity and certainty about those demands is another, arguably more plausible, explanation.

One difficulty lies in the fact that ethics requires not only to do the right thing, but concurrently to do it right. Compliance with a requirement (e.g. parents gave consent, patient has been consulted) is not enough to deem that a child’s recruitment was ethical. Conformity with a set of rules or principles can be achieved only by showing some level of integrity and judgement; by engaging with colleagues and families in a true and sincere deliberation about study settings’ relevance to the research question and appropriateness to each individual child’s situation. But how to report on these constant efforts and, more importantly, how can we be confident in their adequacy? Based on a ten year systematic literature review, this article summarises the current knowledge on normative and empirical demands, as well as obstacles, to warranting that a child’s inclusion is ethical and to preventing moral discomforts. Our review aims to help investigators identify the relevant issues for their studies and to report on how they tackled them. For instance, to preclude access to experimental compounds off-trial can be right; but reasons for it must be compelling enough (safety, scarcity, etc.), so it cannot be analysed as a means to coerce participation, which is inappropriate.⁴

Henry Beecher contended: “an experiment is ethical at its inception; it does not become ethical *post hoc*”.⁵ Likewise, a child’s participation is not ethical based on its consequences, be they positive (clinical response, family’s satisfaction) or negative (absence of response, adverse event); inclusion must be ethical at the time of the decision-making, not retrospectively. For this reason, our review covers all ethical aspects tied to paediatric cancer clinical trials, from design to completion, and the shared decision whether to participate. We aim to guide professionals to identify the main decision nodes and bottlenecks, as well as the proper attitudes that enable families to make a safe, competent and satisfactory decision. A secondary aim is to highlight those areas that are currently evolving or under-documented, and hence the research avenues that are needed.

Methods and material

Search strategy and selection criteria

To answer our research question, we carried out a systematic literature search in MEDLINE®, fitting stringent time (10 years) and topical (paediatric oncology research) selection criteria, without discriminating on each article’s nature nor methodology. Although it induced a higher level of “noise” (recall being privileged over precision),⁶ this approach aimed to accurately reflect the developments in research ethics within the paediatric oncology community.

Research question was translated into the following search algorithm: (((((((oncolog* OR cancer OR hematol* OR haematol* OR leuk* OR malign* OR neoplasm*[Title/Abstract]))) AND (((clinical trial* OR clinical investigation* OR research[Title/Abstract])))) AND ((child* OR adolescent* OR minor* OR young people OR pediatr* OR paediatr*[Title/Abstract]))) AND ((ethic* OR moral*[Title/Abstract]))) AND ("2003/01/01"[Date - Publication] : "2013/12/31"[Date - Publication])).

MeSH® Terms were not used, still to privilege recall, and, to warrant adequacy, keywords were defined following a 4 steps scheme adapting the validated PICO strategy to the needs of a systematic ethical review, namely:

- Environment = Oncology
- Topic = Clinical trials
- Agents = Children and adolescents
- Norms = Ethics

This search gives 423 hits. Given intrinsic lack of precision, a mixed systematic and hand selection based on titles, abstracts and keywords has been carried out following the above ‘ETAN’ criteria:

1. Title selection, based on Topic broadly construed (biomedical research).
2. Inclusion of articles containing Environment AND Agents in title, abstract or keywords.
3. Exclusion of articles when neither title, abstract, nor plain text, showed evidence of a particular emphasis laid on one of the ETAN components.

We cleaned up our database and paid special attention to articles still lacking either abstract or keywords after cleaning (n=13). A supplementary screening of excluded articles allowed to manually include three relevant articles.⁷⁻⁹ Finally, one article has been snowballed in the ‘assessment’ sample,¹⁰ for it was commented by another article fitting all inclusion criteria,¹¹ and one article could not be retrieved.¹² Our literature retrieval strategy is summarised in the supplementary figure 1.

Methods and analysis

We assessed our literature sample using a reference conceptual framework scoping the ethical aspects of clinical trials involving minor patients into 46 items, based on a literature review on

research ethics non-specific to paediatric oncology, carried out in September 2012 and updated in October 2014, within the ethics work-package (WP18) of the EU-FP7 ENCCA project (www.encca.eu).

The preparatory literature review was designed in order to draw a comprehensive overview of the ethical issues susceptible to arise in the intersection of research ethics and paediatric ethics. The search was performed in medical as well as social and legal sciences journals without lower time limit and until 2013 (552 articles examined, out of 3666 hits and 698 after title selection). Ethical issues addressed in the selected articles were listed in a generic wording until reaching saturation (any issue raised susceptible to fall within the scope of another, already identified). Results of this scoping exercise did not fit the purposes of a systematic review for the variety of clinical contexts jeopardised transposability to paediatric oncology and only a narrative account of the results would have been possible (with a random attention paid to the numerous articles retrieved). However, this scoping exercise had two meaningful results relevant for the purposes of the present systematic review:

1. to identify a reference conceptual framework composed of 46 ethical issues;
2. to define these issues prior to the assessment process, in a view to warrant that these issues are mutually exclusive and to minimise dependence to authors' terminologies.

Various ethical issues are addressed in any article and usually, to make a point, authors need to articulate different concepts together (e.g. consent, autonomy, preferences, values, authority...). Thus, to count words does not allow to identify the ethical issues at stake in our literature sample. The minimal unit here has to be the 'ethical argument', namely a sentence, or a couple of sentences, that is minimal to isolate a self-sufficient line of reasoning and allows to characterise the author's stance on the different topics he addresses. Each article was assessed in the light of the 46 reference ethical issues, according to the following rating system:

- 1= the issue is mentioned in the article (no analysis)
- 2= the issue is addressed in the article (at least one dedicated paragraph)
- 3= the issue is a central topic in the article (at least one dedicated section)

To avoid double counting, only highest ranking per issue was recorded for each article. Likewise, as six articles addressed the same subject (i.e. the return of research results), by same authors, based on a unique research programme, only the first article was analysed in order to avoid undue bias on the results.¹³⁻¹⁸ This is not to say that these articles are redundant; but to include all of them would have led to hold this subject as being prominent although it is scarcely addressed over the period.

Results.

Baseline cases

Before analysing our literature sample and highlighting the major outputs in paediatric cancer ethics last decade, we would like to briefly outline three illustrative cases excerpted from our sample, for they provide baseline clinical situations to which we can refer in order to exemplify the sophisticated issues addressed by the authors and show their clinical relevance.

First case relates to parental reliance on medical expertise.¹⁹ Rob is 13, sedated but conscious, diagnosed with an acute lymphoblastic leukaemia. His father and his paediatric oncologist discuss the options of either participating in a four arms randomised clinical trial or giving him standard therapy. Father does not wish to receive and discuss to full information and urges the doctor to make the decision about a suitable course of action: "*Whatever you think is best for my son, I'll do it. I'll sign anything!*"

Second case describes the difficult task of building partnership.²⁰ A boy, who we will name Alberto, is diagnosed with neuroblastoma at age 3 years and dies after 3 years of treatment. His young parents are described as “desperate” due to his diagnosis and poor prognosis. Occurring soon after diagnosis, the offer to enter their child in an upfront randomised trial may jeopardise their nascent relationship with, and confidence in, the medical team.

Third case is about the consequences of research participation.²¹ Joey, 12, has a medulloblastoma. Surgery allowed partial resection and Joey is eligible to participate in a de-escalation study testing low-dose radiation followed by high-dose chemotherapy. Joey’s parents are afraid about the risk of losing a chance of cure but insist on their son’s maturity and capacity himself to decide. Doctor rather emphasises on the need for a family consensus “when you’re facing a possibly life-changing decision”.

Sample characteristics

The three baseline situations above are the only case studies found in our literature sample. Our sample shows a good level of evidence, including empirical studies (33%), feature articles (31%) and review articles (19%) for the most part. Opinions (13%) demonstrate a dynamic reflection ongoing in paediatric oncology, while case discussions are marginal (4%, n=3).

The following relevant quantitative features can be outlined. The trimmed mean of items per year is 7·1, if we exclude the extremes (2004=12; 2008=2). European authors contribute significantly less in our sample than North-American authors (28% versus 69%); only two items stem from another region (Australia). Ethical issues are mostly dealt with in a generic way (55%), with specific attention paid quite equally between early phase trials (24%) and randomised trials (21%).

The qualitative analysis of our results is summarised in figure 1 (also see the supplementary figures). Consent (33%) and research ethics (27%) are the most frequently addressed ethical domains in the field paediatric oncology over the past decade, compared to professionalism (18%) and public policy (15%); ethical evaluation of research protocols (7%) is the least documented field in our sample. Interestingly, the most extensively addressed issue is professional attitude and communication in the recruitment process (value=69); with the duty to care issue (dual role of carer and researcher), it represents 68% of the documentation tied to medical professionalism. Hence, authors essentially focus on the encounter with patients and families at the expense of professional issues related to interactions with peers and the society. Expectedly, all issues tied to consent are extensively addressed (trimmed mean=35·5), mainly in a way to improve the fit with current informed consent standard. This should not obfuscate two important results, namely 1° ethical issues are addressed comprehensively, reflecting a wide variety of stakes (trimmed mean=18·9), and 2° attention paid to research ethics illustrates that ethical and scientific aspects of clinical research are interwoven, for instance studies’ risk-benefit profile is the third top ethical issue (value=56) and involves both technical and value-related dimensions.

Consent

The baseline cases show the difficulty to get “informed, prior and free” consent in paediatric oncology. Issues prominently addressed in this topic are competence, information and understanding.

Competence is addressed in the view of parents (capacity to make surrogate decisions)^{22,23} and child (growing ability to deal with complex information and show proper preferences).^{24,25} Parents and children have proper vulnerabilities.²⁶ Parents are unequally knowledgeable,^{19,27} a reason why Rob’s father refuses medical information. But to focus on this aspect of competence is misleading:

although Joey's parents are not more knowledgeable, their attitude shows that only the child's growing capacity to make choices can limit parental power to make decisions.^{8,28} Information, and cancer experience,²⁹ enables families to fully exercise this right to self-determination. The "information" requirement is addressed in a 'formal' (content) and in a 'material' way (meaning). Some core information *must* be conveyed otherwise consent is invalid³⁰ and useful lists of necessary information are drawn.^{8,23,31,32} Rob's doctor too strongly relies on this formal approach to information, telling the father: "*I know you don't want to be told all the lingo. But I do need to tell you. (Laughs) And I know you're not gonna completely understand this.*" Appropriate information requires to establish a true dialogue and communication process (not a mere transmission),^{1,33,34} allowing to tailor information and secure its meaning.^{7,20,35,36} Family needs shall guide this dialogue,^{30,37,38} only one parental preference cannot be accommodated: the wish not to be informed.

Despite good communication, accurate understanding is difficult to obtain in daily practice due to various obstacles,³² mainly emotional and psychosocial factors,³⁷⁻³⁹ clinical technicalities or study design.^{29,35,40} Authors outline categories ("therapeutic misconception", "therapeutic misestimation", "unrealistic optimism") to discriminate a serious misunderstanding making consent invalid from attitudes merely reflecting preferences (risk aversion) or mindset (hope, optimism).^{28,33,41} Urgency to decide soon after diagnosis is a known aggravating factor,^{27,42} even if randomisation – a research aspect which is difficult to understand – is planned at distance from inclusion (three months in Alberto's case). Despite these difficulties, authors mainly endorse the standard consent conference. They mostly focus on interventions which might improve quality of parental consent (stepwise approach, nurses, leaflets, videos, individual or family conference).^{32,36,38,39,42-44} Only two alternatives to standard consent settings are addressed: 1° 'staged' consent (to obtain consent to randomisation at distance from inclusion)²⁰ and 2° 'differed' consent in emergency-like situations (waiver of consent at inclusion).¹⁹

Closer attention is paid to the following issues: voluntariness of participation, impact that seeking consent can have on patients and parents, and family dynamics. Only Joey's parents truly construe research participation as optional; Alberto's parents would value hospice care but hope for a cure if their child lives long enough through the trial. Likewise, research participation is often experienced as a choice out of necessity.^{1,26,31,35,40,43,45} Phase 1 trials, often seen as last chance for controlling the disease, and correlative biological studies²³ raise particular issues in this regard; for instance, it is argued that families should be offered the choice to opt for trial participation while refusing correlative (non-beneficial) studies.⁴⁶ Hence, offering research participation can have clinical and personal impact, both on patients and parents, either positive (better follow-up, improved self-image or sense of control, "a glimmer of hope")^{21,36,47-49} or negative (health insurance coverage, anxiety or remorse, medical futility or broken alliance).^{24,26,29,30,32,38,45,50,51} Joey's mother is scared by the de-escalation study, anticipating guilt feelings in case of negative results. Negative impacts might be monitored by measuring regret, satisfaction or trust.³¹ But inclusion offer can also impact on family dynamics, by causing intra-familial disagreements.^{24,27,28,47,52} In case of child's refusal to participate (while parents desire participation), the child's views should prevail in phase 1 trials^{1,50,52} while participation against the child's wishes remains permissible when in the child's best interest (defined as the prospect of getting a direct benefit from participation).^{21,50,53} If Alberto was older and refused participation, his case might instantiate the latter point (the alternative mentioned in the case vignette is "to return home [...] with only pain control treatment and nursing support"). However, although legal provisions are clear about the precedence of the 'best interest' clause over minors' interests to self-determination,⁵³ this involves a risk of medical paternalism and professionals should make every effort allowing to reconcile family members' views.²¹ Assent thus also plays a key role in the prevention of "family coercion".³¹ But the risk of causing intra-familial disputes reinforces the

soundness of Joey's doctor remark about the importance of family consensus. It is also necessary to respect patients' own trajectories, by acknowledging maturity and "moral development" or "developmental regression" and preference to defer decisions to parents.^{8,52,54}

Professionalism

Care and research are intertwined in paediatric oncology,^{23,55} which might blur oncologists' roles as doctor and investigator.^{4,32,35} For this reason, duty to care is addressed in a clear normative way: always clearly distinguish between care and research aims and interventions, and patient's interests shall always prevail over research interests.^{1,20,31,54,56-60}

Paediatric oncology research remains exposed to two major difficulties. First, care and research remain in irreducible tension,²⁴ because doctors might be prevented from prescribing a treatment off-trial⁴ or randomisation impinges on personalised care.⁶¹ Second, doctors need to remain highly cautious about the risk of inducing participation due to their dual position^{35,42,58,62} or pro-research attitudes (e.g. belief in a "trial effect").^{52,63,64} Authors therefore focus on recruitment's quality.^{33,43,61,64} Without mentioning other sources of information,^{26,30,39} professional communication requires active dialogue and partnership with parents and patient.^{19,20,28,31,34,47,49,56,65} Non-hierarchical communication, by privileging open discussions and pedagogy,²⁰ aims at correcting asymmetries of information (about technical aspects and family preferences). It is deemed efficient to enable decision-making,^{1,39} to foster alliance,^{21,35,47} and to restore voluntariness by promoting parents' and patients' agency and sense of control.^{34,49} Alberto's case shows that offering research participation may jeopardise confidence in medical expertise²⁸ but appropriate communication is reported effective in this case: "*with increased attention from us, their doubts were mitigated.*" Although training and techniques can help,^{21,34,39,56} communication first requires lay virtues (empathy, consistency, truthfulness).^{40,42,44,57,66}

Except for one series of articles,¹³⁻¹⁸ little attention is paid to the return of research results to participants, although this issue is ethically challenging, especially with intensification of genetic research, and can be important to honour participation or to fulfil patients' right to know.^{23,27} Reward or benefit sharing issues are marginally addressed.^{47,67,68}

Professionals' obligations towards peers and the society are scarcely addressed. Proper completion of studies requires adequate scientific management and appropriate scientific conduct.^{10,69,70} Improving scientific management is seen as benefiting both patients and research,^{41,61} and scientific conduct as a matter of integrity and responsibility.^{41,45} Integrity can be defined as the ability to "shuttle between clinical care and research duties";³² it requires risk-minimisation, benefit-maximisation, and even to refuse inclusion if consent is inadequate.³³ For example, Rob's father attitude, refusing to involve in a true informed consent process, shall be construed as a refusal to discuss the research option. Responsibility is conceived as a shared commitment for cooperation, quality of research,⁷¹ and "optimal use of patient population".¹⁰ The issue of scientific publication is barely addressed in our sample.^{72,73} Regarding broader social context, data ownership or whistleblowing in case of research malpractices are not addressed. Some developments can be found about few professional duties towards the society, such as transparency, viewed as a trust factor,^{35,57} or effectiveness,⁷¹ defined as the ability to maximise the outputs, which includes to foster collaboration with all stakeholders.¹⁰ Finally, social environment is mentioned as a factor that can limit researchers' obligations towards participants in various ways, due to "scientific considerations", "regulatory constraints" or third-parties' rights.⁹

Ethical evaluation and State interventions

Baseline cases illustrate two important results so far: invitation to participate in research is hard to refuse and has the potential to disrupt key dynamics (inside the family or with the medical team); professionals are responsible for enabling families to make the final decision about participation, by “creating a climate of collaboration” and by giving them “the freedom and support to say no”.^{41,49}

Review bodies’ “responsibility to ensure that the study’s risks are justified”⁴⁵ can mitigate this tension, by securing parental and professional roles.⁵² Ethical assessment is made following general (assent and consent, benevolence, non-malevolence, justice and dignity)^{22,43,50,54} or ad-hoc principles (feasibility, risk-minimisation, benefit maximisation, a risk-benefit profile comparable to alternatives, research interventions commensurate with patient’s experience).^{23,46,74} Despite efforts to follow these principles, two main limitations impinge the soundness and relevance of ethical assessments, namely their perceived exteriority (“I would really want to know who those people are”),⁵⁷ and their intrinsic variability, for they include comparisons (“alternatives”) and valuations (“prospect of important direct benefit”).^{8,23,46,54,69} Empirical data shall contribute to improve the consistency of ethical evaluations.^{47,68} A major uncertainty is about whether ethical evaluation should be centralised (emphasis on expertise and equal protection) or kept local (emphasis on flexibility and adaptability).^{50,68,69,75,76} Beside initial review, a strong recommendation is made as to secure the ethical conduct of research, namely to develop education and training, mainly in research ethics and communication.^{8,11,20,30,34,36,39,48,53,56,64,70,71,76} Additional recommendations include onsite audits and support in conflict resolution, guidelines, and monitoring.^{35,54,70}

Another issue relates to the need of national and international cooperation.^{11,32,41,45,60,69} Despite international or regional regulatory instruments,^{10,23,45,56,69,76,77} discrepancies remain between US, European and national legal orders.^{27,29,46,50,53,69,70,78} Authors tend to privilege guidelines and incentives (soft law) over harmonisation (hard law) as to unify research practices.^{10,11,21,22,27,41,54,60} Barriers to paediatric research are first tied to policy inadequacies; authors mention burdensome or unclear regulatory demands, or deficiencies in the health system’s management (e.g. ineligibility of research participants to hospice care).^{26,28,46,51,69,70,76} Other barriers relate to specifics of paediatric oncology (access to new compounds, small populations).^{10,11,22,24,74,78} A policy shift is identified from conditionally allowing (as an exception), to positively encouraging, paediatric research.^{28,68} This shift implies to reconcile the two legal logics of protection (safeguards, hard law) and of innovation (incentives, soft law).⁸

Finally, research situations involve connate legal fields, especially fundamental rights of the child (to physical integrity, to privacy and self-realisation)^{21,23,27,32,41,42,45,54,63,69} and of his parents (to respect for family life, values and parenting styles).^{19,34,47,50,54,66,69} These rights can conflict, as for instance if Joey’s parents had refused to involve him in the decision. Two main results about the articulation between child’s and parental rights are that child’s assent can hardly be dispositive (“parents are experts on the patient”)²¹ but child’s best interest overrides deference to parental authority (as in the case of a mature minor denying participation in phase 1, where prospects of direct benefit are unpredictable).^{21,50} Two other connate legal fields are scarcely addressed: property rights^{27,57,68} and financial interests.⁵⁷

Research ethics

Paediatric cancer research remains a field exposed to steady moral dilemmas, mainly tied to exposing patients to research risks while they are unable to consent^{24,28,41,77} and to informing without negating hope nor creating unrealistic expectations.^{23,45,48} Against allegations of sheer amorality in the 1970s,^{41,53,58} authors hold paediatric research as ethical but develop different moral justifications

and attitudes, depending on whether they insist on child's prospect of medical benefit, on broader child's interests that can be promoted through research participation (education, self-realisation), or on social benefits from, and reciprocity value of, research.^{1,28,45,62,63,77} Lack of common definitions on technical or moral notions is another source of ethical uncertainty.^{40,50,64,69} Empirical ethics⁷⁹ surveys report following parents' and patients' attitudes: a majority are supportive of research for a variety of reasons, including trust in clinicians;²⁹ they find it hard to refuse participation and often feel disappointed when randomised in the standard arm;³² a majority does not see participation in phase 1 trials as "a decision";⁶⁶ parents vary in their willingness to have control over decisions.³⁶

Professional attitudes are also documented: professionals value proxy-consent,⁷⁹ are strongly confident that research participation is beneficial to patients ("trial effect")^{41,48} and "prefer the perspective of a therapist over that of a researcher";³² accordingly, they might underestimate patients' ability to participate in decisions.^{52,55} Our sample shows no study on lay public's views on paediatric research.

Molecularly targeted therapies¹⁰ raise specific issues such as the justification of non-beneficial associated biological studies,^{22,46} the clinical significance – and benefit value – of molecular endpoints,^{46,58} and the need to carry out research in children without pre-data in adults.²² Long-term outcomes^{22,46} involve ethical issues tied to epidemiological research²⁷ and quality of life measurement.⁷⁰ Other issues are rather phase-specific, although baseline cases suggest that these can also arise in different settings. Main issues in Phase 1 trials are: scientific justification,^{3,22,45} "net risk research",^{23,48} lack of benefit due to underdosing,⁵⁸ and "therapeutic misconception";²⁸ in Rob's case, father's attitude may be interpreted as an instance of therapeutic misconception outside phase 1 since he conflates a research objective (to compare four strategies) with a therapeutic decision ("whatever you need to do, do it!"). In phase 2 trials, belief in the supposed efficacy of a new agent is problematic if it leads to use drugs off-trial or to overestimate the prospect of benefit;²³ in Alberto's case, parents' motives ("they ... nurtured the hope that if he lived a few more years a cure might be found") suggest a correct estimate of their child's prospect of benefit, making consent valid despite their difficulties to cope with distressing information. Two issues are mainly addressed regarding phase 3 trials: treatment depersonalisation inherent to randomisation^{32,75} and clinical uncertainty about comparators' superiority ("equipoise").^{23,72} This notion is difficult to convey: while "uncertainty" is the reason why research is scientifically needed and ethical, this is also why Joey's mother deems participation unreasonable since doctors do not know whether de-escalation will prove safe enough ("I can't say yes to this experiment; I just want our son to live").

On this background, it is argued that, compared to a fixed approach to study design, alternative designs²² may allow to better fit ethical requirements to risk-minimisation (pre-clinical data and modelling, Bayesian approaches)^{11,41,46,60,78} or benefit maximisation (prioritisation of new agents, post-trial access to drugs),⁷⁵ to commensurability to child's medical experience (inclusion of palliative and hospice care components in phase 1, minimise travels, stays or correlative studies),^{40,51,58,66} and to valid consent (delay randomisation).³⁵ "Equipoise" is also addressed in different ways:³⁵ although community uncertainty remains the proper "ethical foundation" for research,⁷² doctors and families should also achieve a state of indifference about the comparators in child's situation.¹⁹ Personal approaches to equipoise remain questionable yet, because investigator's opinion might bias inclusions and requiring "parental equipoise"³² might unduly dismiss plausible parental motives, such as the empirically shown usual preference for the experimental arm.

Ethical debates remain vivid and evolving, especially on three ethical issues. Access to clinical trials, although not a central issue in our sample, evolves over the decade from a population-based (children and adolescents are 'therapeutic orphans')^{22,24,68,75} to a rights-based argument (claim to

access new compounds);^{23,28,32,33,41,50,58} this fairness issue evolves in two directions, namely of fair selection and equal opportunities,^{58,62} and whether families should be allowed to elect the experimental treatment alone (either in- or off-trial).⁴ Another issue, studies' risk-benefit profile, is extensively addressed.^{19,24,28} Risk-benefit calculation is by nature tentative and hypothetical in research,^{1,23,52} so risk-minimisation is a basic ethical requirement in paediatrics⁷⁷ without precluding the possibility of net-risk research.^{39,53} Risk-benefit balance must be assessed in patient's perspective^{41,45} and comparatively,⁵⁰ which means to aggregate burdens of participation to risks and to draw comparisons with *all* alternatives, including non-participation or the possibility to access the experimental treatment off-trial.⁴ A careful calculation can guide design optimisation⁶⁹ but the decision whether the ratio is worth participating necessarily entails a value judgement, which belongs to the patient and his family,^{21,40,43,47,66} given the variability of parental attitudes, "complex trade-offs"²⁶ and the "interconnected nature of family decisions":⁵⁴ Joey's mother is risk-averse but agrees on the importance of knowing his preferences; Alberto's young parents would value hospice care at home but the prospect of additional survival, and hope for a cure in the meantime, makes them decide differently. Finally, altruism remains an intricated issue^{27,31,61} in paediatric oncology because, if research is of greatest social value, it is uncertain whether parents can ever "think beyond the interests of their child".³² In some situations however, as in Alberto's case or in phase 1 trials, given the unlikelihood of individual benefit, other motivations except altruism might reveal a misconception.⁷⁷ Therefore, authors develop several reasons why it would be excessive merely to dismiss altruism (motivational value, ethics of reciprocity, self-image).^{28,59,66}

Discussion

Examples from, and interpretations of, the three baseline cases are ours, as they nicely illustrate the wide range of ethical issues encountered. These cases show the importance for professionals, parents and patients to be clear and confident on the reasons why they agreed on research participation. As evidenced by the positive or negative impact it can have,⁴¹ offering research participation is not a trivial matter in paediatric cancers care journeys. Our review allows us to outline three current challenges.

One challenge is normative. Unethical behaviours do not need to be observable or malicious to be worth reflection. Hence, how to reflect on the pitfalls of consent, such as professional inducement or family coercion, without this being ill-perceived as unduly suspicious? Ethical reflection needs to develop inside the paediatric oncology community (including patients' representatives), to highlight stakeholders' expertise. Empirical ethics is one example in our literature sample of successful integration, despite a difficulty to draw general conclusions from individual studies. Clinical ethics builds bridges differently, offering support to stakeholders without intruding in their agency. Philosophical methods to deliberation (e.g. the "reflective equilibrium" approach)⁷⁹ allow to involve all stakeholders in ethical knowledge generation, in a view to collectively define solutions to daily dilemmas. Within the EU-FP7 European ENCCA project, a dedicated work-package allowed to build and maintain partnerships on ethics and to conduct participatory research with professionals and patients' representatives from the European branch of CCI (www.iccpo.org).

A second challenge is practical, namely: how to satisfy the need to document consent ("to sign") without obfuscating its very nature as a complex and subtle process of human communication? Difficulties to fit the stringent informed consent standard, showed by empirical studies,^{27,31} demonstrate the need for supporting a constant community dialogue on ethical matters. It is not enough to show inaccuracies in families' understanding retrospectively;⁶⁴ there is a need to deliberate on effective interventions to improve the situation, in a view to identify patient's and

parents' decisional needs⁵⁵ and to redress serious misunderstandings *during the consent process*, in a view to prevent invalid consent but also to avoid undue vetoes on family choices.^{30,38,58} Categories as "misconception", "misestimation" or "optimism" set useful distinctions in this direction: hope⁶⁶ in a phase 1 trial is problematical if parents misestimate their child's odds to benefit, not if they strive to keep a strong fighting spirit against cancer.^{33,63} As decision-making about research participation is irreducible to a token of rational thinking, ethical theory needs to be informed by professionals' and families' experience while drawing such distinctions. For instance, although the aim of a phase 1 trial is to study toxicity, everyone – families and carers – hope for a tumour response. This motive remains questionable and shall never override other ethical considerations⁶² but to merely dismiss it would overlook the importance of taking any chance against cancer⁵⁸ or rare examples of successful tumour resection after a phase 1 trial.

Thirdly, community ethical reflection and deliberation should develop in three directions. First, it has been shown how difficult it is for families to clearly grasp the optional nature of research participation. In this domain, other avenues than improving professional practices might be explored at society level. For instance, to heighten general public awareness⁶⁸ about research at the level of organ donation might alleviate a portion of the decisional burden on families once compelled to make a choice in an "agonising situation".³² Second, any effort to intensify research (clinical, biological, epidemiological) in rare conditions increases the demand on families to accept or to refuse participation; appropriate consent rules and practices must be defined, in order to avoid multiple requests where it does not increase children's protection. Third, current developments in cancer research, in specific molecularly targets (e.g. N-Myc gene amplification in neuroblastoma) or in conditions which are rarer in adults than in minors (e.g. Ewing sarcoma), call to reassess long-standing ethical consensus, such as no research in minors without pre-data in adults.

Conclusion

Some ethically challenging situations, even common ones, may have been overlooked. For instance, we did not identify any particular attention paid to the case of disagreement among professionals. A reason may lie in an oversimplified schematisation of the communication process with families, which disregards the discussions among professionals prior, or concurrently, to the dialogue with families. Professional perspective is often encompassed within a "relational triangle" in paediatrics, involving parents, child patient, and a single "physician" or a presumably consensual group of healthcare professionals.^{1,34,60} Clinical ethics offers more sophisticated models of deliberation and dispute resolution on the ward, and maybe a caveat is to be made here, due to our focus on research ethics as opposed to bedside ethics. Readers can find useful guidance in the above developments, though. With regard to the duty to care, the offer to participate in a trial must necessarily ensue from a thorough multi-professional assessment of its adequacy to child's clinical situation. Accordingly, the physician offering inclusion must be confident that participation is compatible with child's interests (just like the alternatives). The reasons for that must be clear to all team members who can accept and endorse the decision (a mark that team discussions were effective). Moral discomforts and clinical disagreements shall be mitigated, and an agreement among professionals shall be negotiated, before inclusion can be proposed to the family.

The same procedure – a multi-disciplinary team meeting applied to ethically challenging situations – should apply when a family requests inclusion or when off-trial access to an experimental compound is considered. When a trial is available, inclusion and/or referral should be decided out of respect for family's preferences, provided that it is compatible with child's interests and insofar inclusion criteria are met. Situations where there is no trial available, or inclusion criteria are not met, are slightly

more complex. Only child's best interest can provide some guidance here, based on the scientific rationale underlying the prospect of some direct benefit from getting the experimental compound. Molecularly targeted therapies may change the landscape here since a strong biological rationale sometimes exists at early stages of development. In addition to a stronger rationale, biology-driven therapies also have a different spectrum of toxicities (e.g. cutaneous or digestive) compared to standard chemotherapies. In this case, access to experimental compounds, even off-trial, is arguably in the best interest of children after all standard therapies failed. But off-trial access should remain the exception, and not a matter of discretion or convenience: clinical efficacy needs to be scientifically established (future generations of patients deserve it) and long-term effects need to be monitored (which is important for current patients too). At the very least, off-trial access should not be a palliative to inadequate eligibility criteria, or inadequate paediatric development schemes, excluding children or adolescents despite a scientific rationale in these populations.

The rise of new research orientations and the multiple facets of daily clinical experience show the impossibility to draw definitive answers and authoritative guidance. However, a careful analysis of ethical developments allows to identify useful milestones and key decision-nodes in the individual and collective endeavour to behave ethically at the different steps of recruiting young cancer patients in research (see table 1).

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Figures and Tables

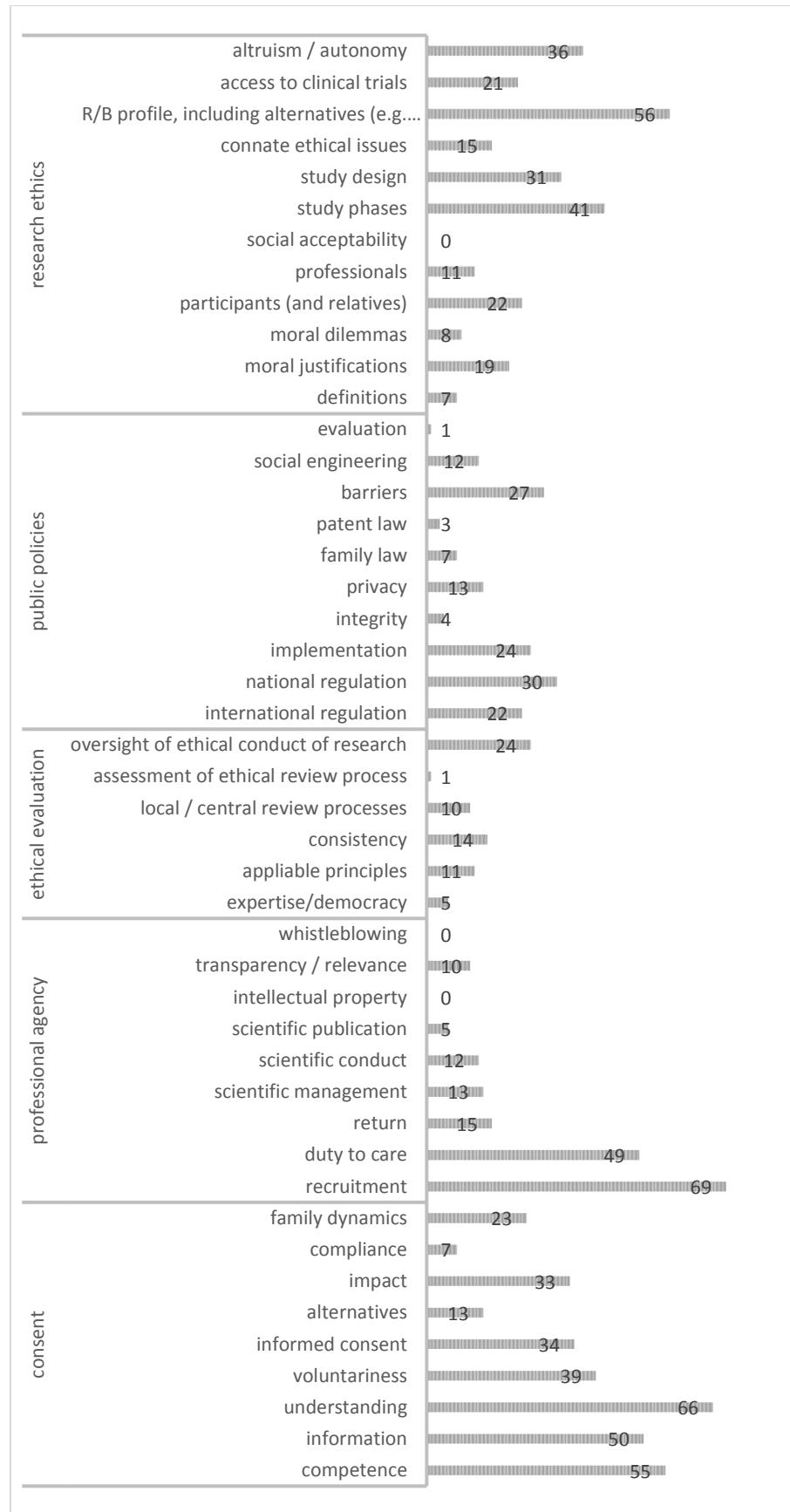


Fig. 1 List of relevant ethical issues (n=46) and their importance in articles included (n=78).

Domain	Relevant questions to address
Research ethics	Research objectives and underlying scientific rationale (strong/weak)?
	Patient representatives' involvement in research conception?
	Is minor patients' participation necessary?
	Which standard-of-care alternatives to participation? Prospects of direct benefit?
	Measures taken to minimize risks and burden tied to participation? (design optimisation)
	Non-inclusion criteria backed on scientifically sound reasons?
	Other settings considered? (e.g. alternative design, staged consent, off-trial access...)
Legal/ethical consistency	Post-trial access or benefit-sharing considered? Return of research results?
	Adequate international/multi-centre cooperation? (optimal study/sample sizing)
	Compliance with national/regional (e.g. European) law?
	Interference between study settings and patients' or parents' interests? Justification?
	Connate legal aspects? (e.g. data custodianship, patenting...)
	Overall ethical justification? (compliance with general principles – e.g. dignity)
	<i>Ad hoc</i> ethical justification? (e.g. commensurability to patients' medical experience)
Professionalism	Adequate study management and monitoring?
	Appropriate study investigators' training in research ethics and communication?
	Proper scientific conduct and prevention of conflict of interests/roles (carer/researcher)?
	Multidisciplinary team meeting and consensus about: <ul style="list-style-type: none"> - commensurability/equipoise betw. participation/alternatives in child's situation? - participation compatible with individual child patient's interests? - opportunity to offer participation to the family? (e.g. linguistic/psych. factors) - (if available) opportunity off-trial access?
	Prevention of professional biases? (e.g. inducement, over- or under- motivation...)
	Adequate understanding of family's needs and values?
	Assessment of family's understanding and expectations (optimism/pessimism)?
Consent	Appropriate consent settings and timing? (e.g. differ consent to randomisation?)
	Quality of information? (content, means, and adaptation to family's needs)
	Enough time for pedagogy and discussions with parents/patient?
	Child involved in the decision-making? (according to age, maturity, and needs/trajectory)
	Did the family carefully consider all alternative options?
	Does child agree with participation?
	All measures taken to secure family consensus? (dispute prevention and resolution)

Tab. 1 Key decision-nodes from study inception to individual child patient's inclusion.

Appendices:

Unstructured summary

Based on a systematic literature review in MEDLINE®, we report on the main research ethics developments in paediatric oncology in the last decade (2003-2013). Current knowledge on normative and empirical ethical demands is quantified and summarised from a list of 46 issues. This primarily aims at providing readers with a comprehensive account of the main decision nodes and proper professional attitudes that enable families to make a safe, competent and satisfactory decision about their child's enrolment, or non-participation, in cancer clinical trials. Our review shows the importance for professionals to engage in a constant reflection on optimal trial designs, to deliberate together on the impact of offering research on key family dynamics, and to understand families' needs and values accurately. In the light of current scientific evolutions, we further emphasize on the need to enhance societal awareness about research in children and adolescents, to prevent 'research fatigue' in small populations due to multiple solicitations or inadequate legal demands, and to reassess longstanding ethical certainties in the strictest view of promoting sick minors' interests. This review allows to draw a sequence of questions to guide and encourage collective and individual endeavours to improve the ethical soundness of our research practices.

Supplementary figures

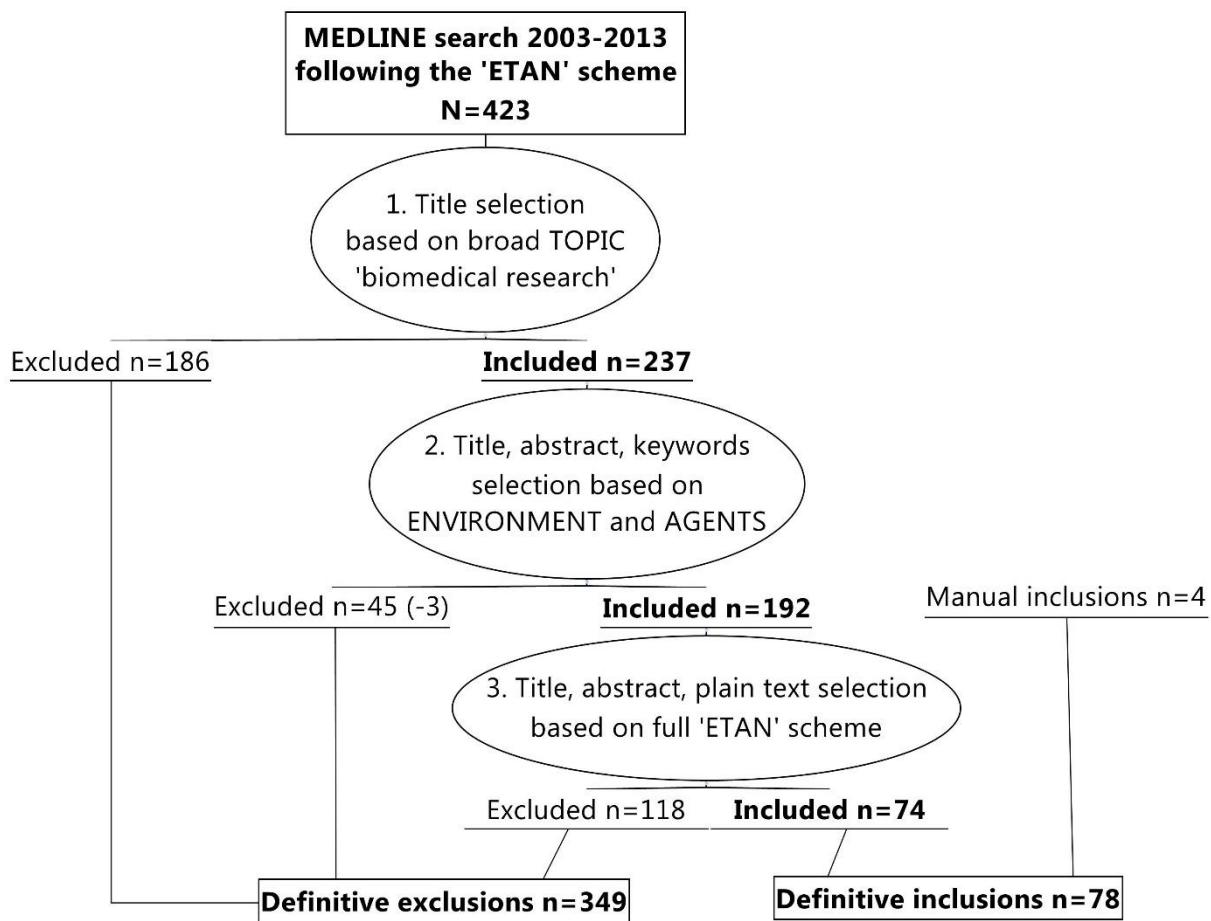


Fig. 2 Literature retrieval workflow.

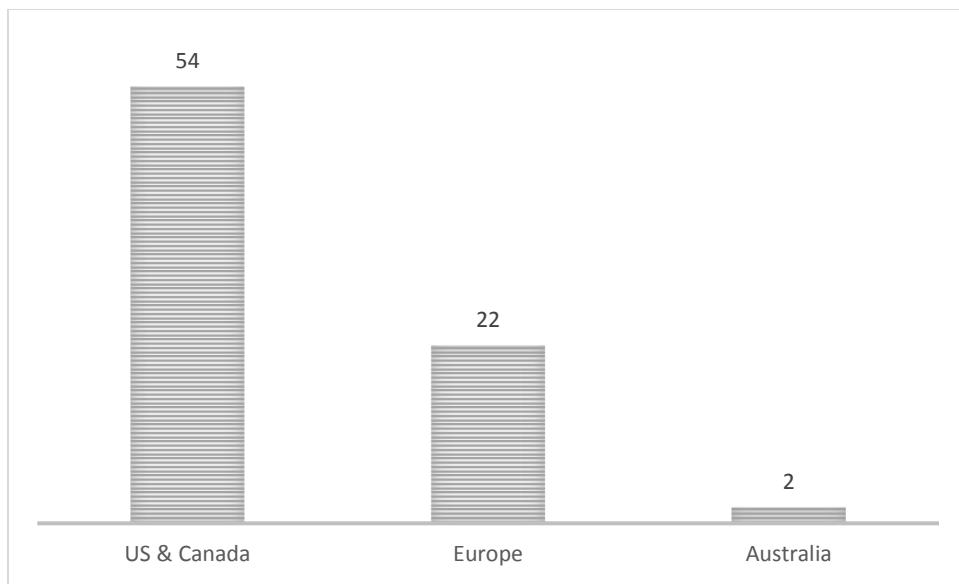


Fig. 3 Geographic repartition of articles included (n=78).

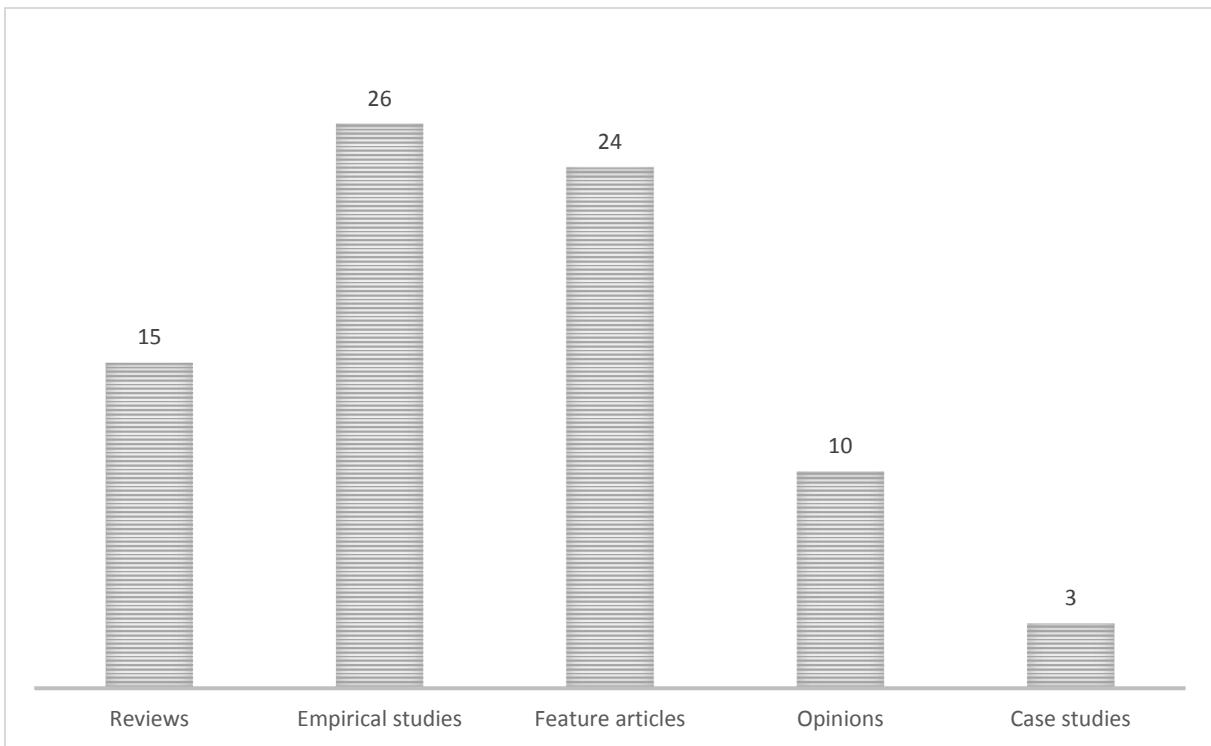


Fig. 4 Level of evidence by article's type (from higher to lower).

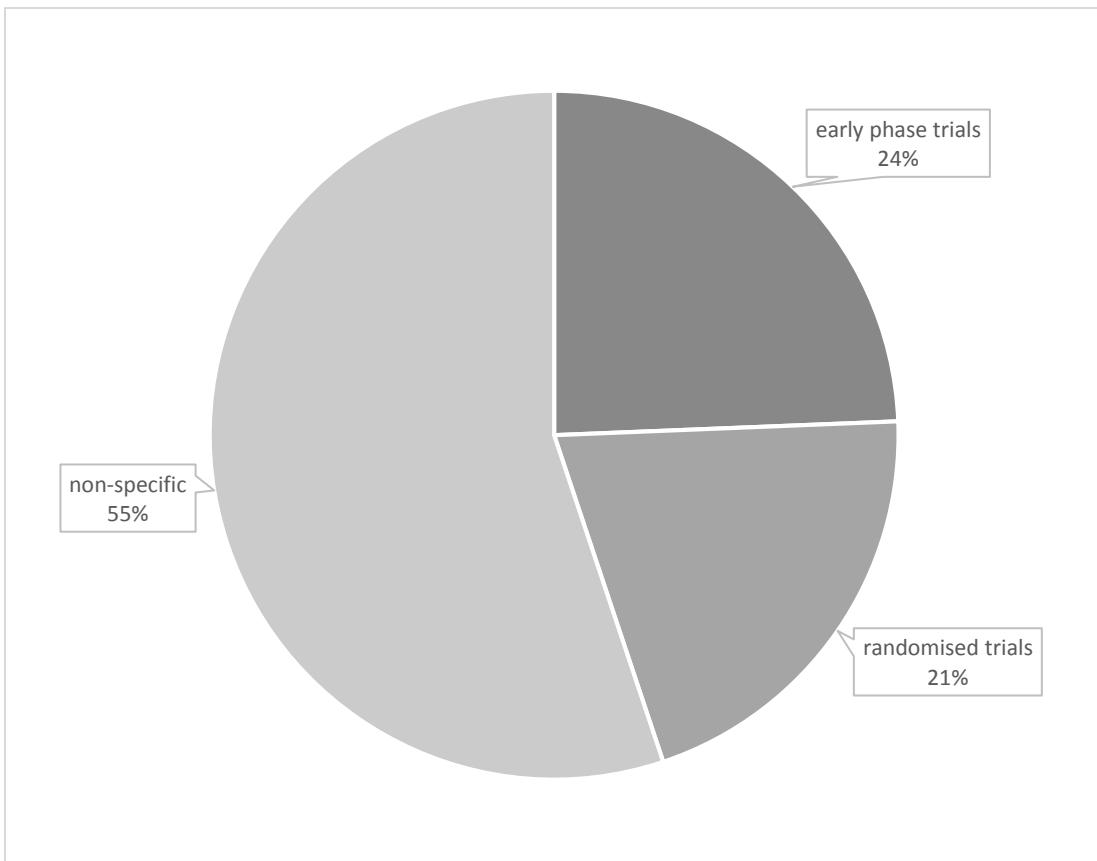


Fig. 5 Phase-specificity of articles included (n=78).

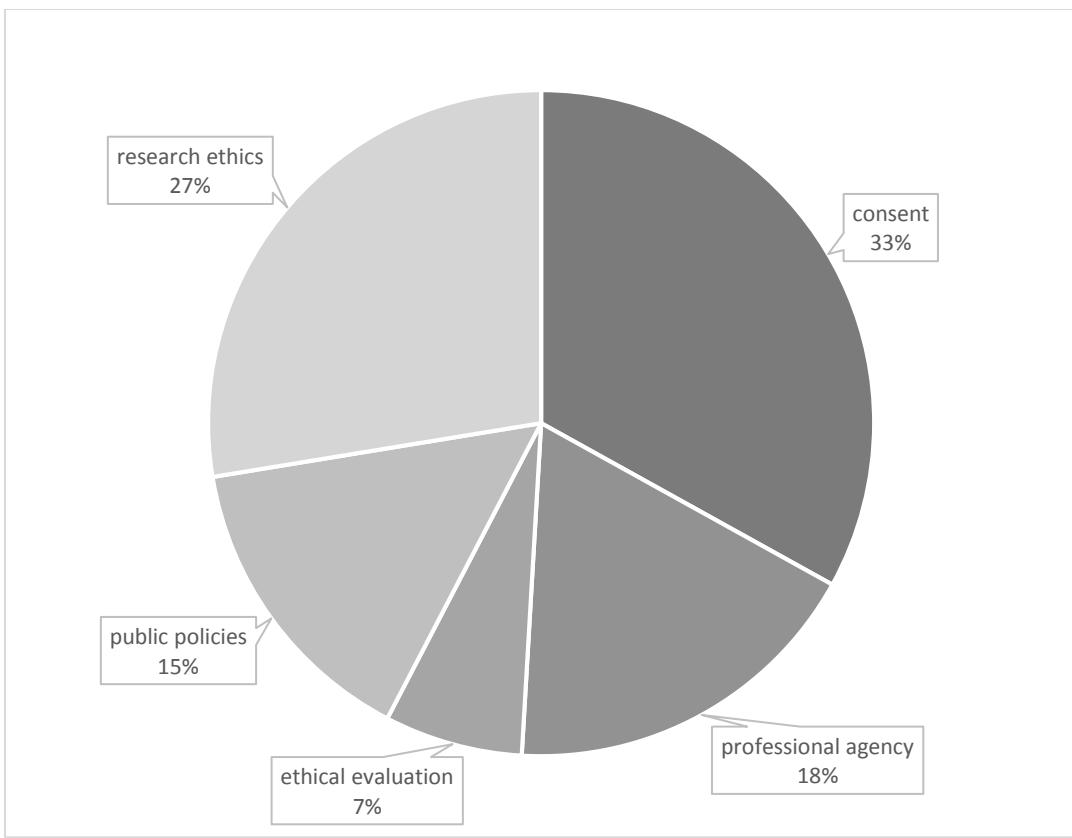


Fig. 6 Domains of ethical debates and documentation last decade (2003-2013).