Ethical principles and practices in paediatric trials: emerging issues

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BEST PRACTICES FOR HEALTH RESEARCH INVOLVING CHILDREN AND ADOLESCENTS

Genetic, Pharmaceutical, and Longitudinal Studies

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The 10 Best Practices

I. INCLUSION OF CHILDREN IN RESEARCH

II. CONSENT TO RESEARCH

III. ASSENT OF THE CHILD

IV. DISSENT OF THE CHILD

V. DEPARTURES FROM CONSENT

VI. EVALUATION OF RISKS AND BENEFITS

VII. PRIVACY AND CONFIDENTIALITY

VIII. RETURN OF RESEARCH RESULTS

IX. PAYMENT IN RESEARCH

X. COMPOSITION OF RESEARCH ETHICS

The Old : Classical Ethical Issues

1. Inclusion of children in clinical trials

Risk vs. Benefits

- Balance between obtaining knowledge and ethical imperative to protect the child and respect his/her integrity and dignity
- Good clinical practice (GCP)

The Old : Classical Ethical Issues

2. Consent to research vs. care

- *Researchers should obtain the free and informed consent of the competent child or, if incompetent, of his/her parents.*

- Reduce the risk of therapeutic misconception
- Ensure that child & parents understand:
- Risks and benefits inherent in trial
- Trial ≠ treatment
- Participation is unlikely to extend survival

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The Old : Classical Ethical Issues

3. Assent

- *Respect for the growing developmental capacity of children to be involved in decision-making process and choices in research during childhood.*
- *To the extent possible, researchers should obtain the assent of the child according to his/her level of development and capacities. When the child develops the legal capacity to provide a fully informed consent or attains the legal age of majority, researchers should obtain informed consent*

The Old : Classical Ethical Issues

4. Confidentiality

In order to ensure that privacy and confidentiality are maintained, researchers should adopt appropriate safeguards, subject to applicable law.

- Longitudinal studies: create additional risk of unauthorized access
- Need for increased security measures and governance

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The Old : Classical Ethical Issues

5. Multi-site Ethics Review

- Contradictory ethics

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The New : Emerging Ethical Issues

1. Return of Research Results

A continuum of policy opinions:

- *Returning at least some results is ethically permissible (and sometimes legally required)*
- *Returning results is typically misguided; fosters therapeutic misconceptions; promotes increased health care costs with few corresponding benefits*

Little "paediatric-specific" guidance:

- *need to address unique issues related to return of results involving minors*

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Return of Research Results – Practical Considerations

- "Tripartite" relationship: researcher - parents – child
- Best interest of the child
- Respect for persons
- Conclusive/Inconclusive results
- Clinical significance/Actionable?
- Type of Disease/Condition
- Delivery of Results (by whom? counselling?)
- Familial context
- Evolving Capacity of the child

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•Conflation between research findings and incidental findings.

•Incidental findings are findings “concerning an individual research participant that [have] potential health or reproductive importance and [are] discovered in the course of conducting research but [are] beyond the aims of the study.”

S. M. Wolf, F. P. Lawrenz, C. A. Nelson, J. P. Kahn, M. K. Cho, E. W. Clayton, J. G. Fletcher, et al., "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations," *Journal of Law Medicine and Ethics* 36, no. 2 (2008): 219-48.

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Modalities of the Return of Individual Research Results:

Table 3

Terms Relating to "Clinical Utility"

"contribute to the current disease status or alter assessment of the future disease risk of the research participant"[26]
"information relevant to the health and wellbeing of the person"[27]
"relevant to their welfare"[28]
"clinically relevant for individuals or their biological relatives in treating or alleviating health conditions or risks"[29]
"important health implications, i.e. fatal or substantial morbidity or should have significant reproductive implications [and] [p]roven therapeutic or preventive interventions should be available"[30]
"information vital to the subject's life"[31]
"immediate and clear benefit to identifiable individuals [that] will avert or minimise significant harm to the relevant individuals"[32]
"pertinent to the improvement of health and/or the prevention of disease"[33]
"significant implications for the subject's health concerns" and "a course of action to ameliorate or treat these concerns is readily available"[34]
""clinically actionable"...the result might not lead to a cure, but it could help the participant better understand a clinical condition or plan for the future"[35]

Knoppers, BM & Dam, A, "Return of Results: Towards a Lexicon" (Winter 2011) *Journal of Medicine, Law and Ethics.*

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Return of Research Results – International Ethical Norms

EMEA:

" Systematic registration of paediatric clinical trials and publication of results including favourable ones, together with a thorough analysis of the literature should allow detection of similar trials, with similar aims, and thus prevent unnecessary duplication of trials in children"

(*Ethical considerations for the clinical trials on medicinal products conducted with the paediatric population, 2008)*

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Return of Research Results – International Ethical Norms

UNESCO:

" Parents remain the guardians, on behalf of their children, of information about them. It is their duty, if necessary in agreement with genetic counselors and pediatricians, to decide to what extent, when and in what form the child be informed about his/her genetic data."

(Report on Confidentiality and Genetic Data, 2008)

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Return of Research Results – International Ethical Norms

Canadian Paediatric Society (CPS) & Canadian College of Medical Geneticists (CCMG):

" Paediatricians should inform parents and children with adequate capacity to understand the information that the reliability and validity of individual research results may vary with the understanding of the gene disorder and its testing. Recipients of this genetic information should be cautioned about acting on research results that may have inadequate clinical accuracy or confidence."

(Guidelines for genetic testing of healthy children, 2009)

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Biobanks and Return of Research Results: Current Practices

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Return of Individual Results– Clause Examples

McGill University Health Centre clause:

"...you and your doctors **will not** get reports regarding the specimens that you submit for this type of research...b/c the value of the research results for any single patient is often not immediately clear."

"...you **will not** receive any reports or information about any other specimens submitted to be stored in the bank or used for future research...b/c often we do not know the importance of the research results for any one single patient."

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Return of Individual Results– Clause Examples

University of British Columbia clause:

"Consequently, it will be impossible to inform you/or your child of the results of the analyses on your own information. You will, however, **have access to the general results** and will be informed of publications arising from the research."

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Return of Incidental Findings– Clause Examples

Children's Hospital of Eastern Ontario clause:

"If we find information by chance that relates to another condition besides the one under study and it is life threatening or very serious and there is a treatment available, we **will re-contact** you **unless you indicate you do not wish to be contacted**... For all other information that may be uncovered by chance...**we will not re-contact** you."

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Return of Incidental Findings– Clause Examples

FORGE clause (Children/Minors):

"... there is a chance we may uncover health information (information we were not looking for) which would directly impact the care of you/your child during childhood. If the study identifies such information, the study doctor **will** inform you/your child."

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Conclusion

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International Cancer Genome Consortium

International Cancer Genome Consortium

- Elucidating comprehensively the genomic changes present in many forms of cancers that contribute to the burden of disease in people throughout the world;
- Generate comprehensive catalogues of genomic abnormalities in tumors from 50 different cancer types and/or subtypes;
- Make the data available to the entire research community as rapidly as possible, and with minimal restrictions, to accelerate research into the causes and control of cancer.

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The Public Population Project in Genomics

- P3G (The Public Population Project in Genomics) is a non-profit international consortium focussed on optimal access and use of population biobanks and databases. The objective is to lead, catalyze and coordinate international efforts and expertise to optimize the use of studies, biobanks, research databases and other similar health and social research infrastructures for the improvement of individual and population health.
- E.g.: 53 studies results: 6 million virtual participants on 223 variables.

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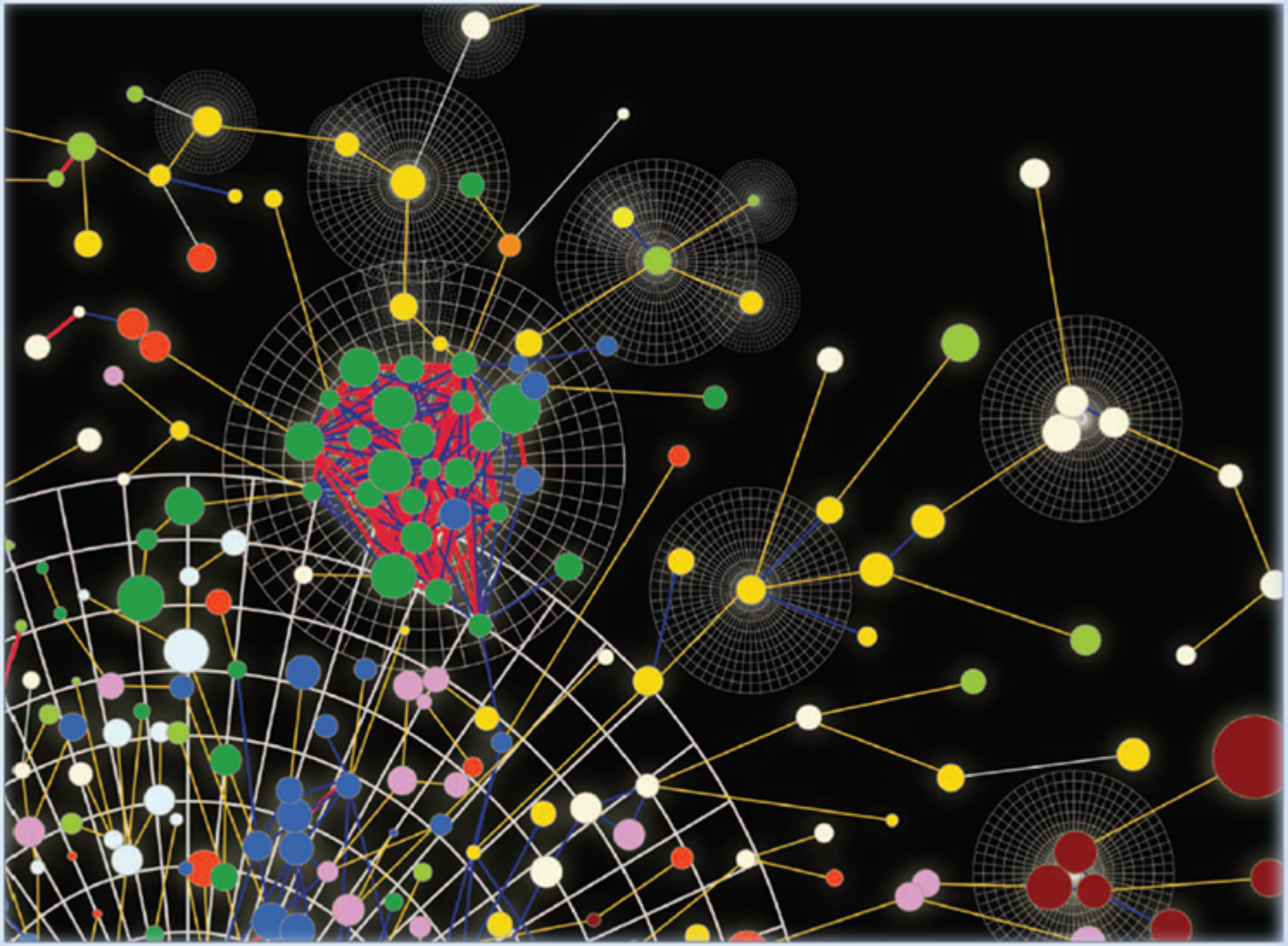

César A Hidalgo, “Thinking Outside the Cube”, *Physics World,* December 2008

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