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Original Research

Impact of COVID-19 in paediatric early-phase cancer clinical trials in Europe: A report from the Innovative Therapies for Children with Cancer (ITCC) consortium



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Received 16 September 2020; accepted 25 September 2020

Available online 9 October 2020

KEYWORDS

COVID-19;
Clinical trials;
Drug development;
Paediatric
haematology and
oncology;
Healthcare policy

Abstract Introduction: Data regarding real-world impact on cancer clinical research during COVID-19 are scarce. We analysed the impact of the COVID-19 pandemic on the conduct of paediatric cancer phase I–II trials in Europe through the experience of the Innovative Therapies for Children with Cancer (ITCC).

Methods: A survey was sent to all ITCC-accredited early-phase clinical trial hospitals including questions about impact on staff activities, recruitment, patient care, supply of investigational products and legal aspects, between 1st March and 30th April 2020.

Results: Thirty-one of 53 hospitals from 12 countries participated. Challenges reported included staff constraints (30% drop), reduction in planned monitoring activity (67% drop of site initiation visits and 64% of monitoring visits) and patient recruitment (61% drop compared with that in 2019). The percentage of phase I, phase II trials and molecular platforms closing to recruitment in at least one site was 48.5%, 61.3% and 64.3%, respectively. In addition, 26% of sites had restrictions on performing trial assessments because of local contingency plans. Almost half of the units suffered impact upon pending contracts. Most hospitals (65%) are planning on improving organisational and structural changes.

Conclusion: The study reveals a profound disruption of paediatric cancer early-phase clinical research due to the COVID-19 pandemic across Europe. Reported difficulties affected both patient care and monitoring activity. Efforts should be made to reallocate resources to avoid lost opportunities for patients and to allow the continued advancement of oncology research. Identified adaptations to clinical trial procedures may be integrated to increase preparedness of clinical research to futures crises.

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1. Introduction

The COVID-19 pandemic has led to a global healthcare crisis, affecting more than 28 million individuals and resulting in 917,417 deaths as of 14th September 2020 [1]. All European states, although not equally affected, have been forced to make unprecedented adjustments to prioritise resources against COVID-19 [2,3].

Although clinical research is key to advancing medical knowledge and improving patient care, priority has been given to COVID-19–related patient care during the pandemic. This has severely impacted essential clinical research in other fields, such as cancer research [4,5]. Coronavirus mitigation measures can affect the conduct of clinical trials in many ways, e.g. patient recruitment, completion of trial assessments, or

provision of investigational medicinal products (IMPs) [6]. Furthermore, pharmaceutical companies have redirected their focus to developing diagnostics and treatments against COVID-19, thus neglecting other research areas [7].

To limit the downstream impact for patients and for the drug industry, the European Medicines Agency [8] and several national agencies [9–11] have issued guidelines on the management of clinical trial activities during the pandemic. They are all aligned in the intention to maintain trial activity, while assuring patient safety and trial activities traceability, but no definitive recommendations have been provided, making it difficult to create a unified action plan. Across Europe, all parties (i.e. healthcare authorities, regulators, sponsors) have implemented different measures depending on the impact of the pandemic in their countries and their capacity to adapt.

Particular attention should be given to patients in cancer clinical trials because of their remarkable vulnerability: cancer patients not only require timely evaluation and treatment that does not allow for delays [12], but also they may be vulnerable to COVID-19–related serious events [13,14]. The European Society of Medical Oncology [15] and International Society of Paediatric Oncology [16] have developed guidelines to mitigate the deleterious effects of the pandemic on the treatment of cancer patients. However, data regarding real-world impact on cancer clinical research during COVID-19 are scarce [17,18].

In this study, we evaluate the impact of the COVID-19 pandemic on the early-phase clinical trial activity in paediatric haematology–oncology in Europe. We analyse the experience of the Innovative Therapies for Children with Cancer (ITCC) consortium, an academic consortium dedicated to improve the access to novel treatments for children and adolescents with cancer in 13 European countries [19,20].

2. Methods

The local representatives from all 53 ITCC centres accredited to conduct early-phase clinical trials in paediatric cancer were contacted and sent a 93-item questionnaire. This questionnaire investigates the impact of the pandemic on phase I/II clinical trials in solid and haematological paediatric malignancies and molecular screening cancer platforms (Appendix 1) between 1st March and 30th April 2020. The online survey was closed on 21st June. Descriptive statistics are provided using SPSS Statistics® (V.23 TM, Chicago). Additional information about the status of the trials was obtained from EudraCT (<https://eudract.ema.europa.eu/>) and the National Library of Medicine clinical trial registry (<https://clinicaltrials.gov/>).

3. Results

Of the 53 ITCC sites, 31 (58.5%) responded, including 22 university hospitals, 6 cancer centres and 3 private hospitals. All responses were complete and could be included in the analysis. Participating sites accounted for 12 European countries, with a fair representation from Northern, Southern and Western Europe. Fourteen sites were exclusively paediatric, while 17 treated adults and children.

Sixty-four different phase I ($n = 33$) and phase II ($n = 31$) trials and 14 different molecular platforms were active and recruiting before 1st March. Phase I and phase II trials and molecular platforms were open in a median of four sites (interquartile range [IQR]: 1–7), three sites (IQR: 1–9) and one site (IQR: 1–3.25), respectively (Table 1).

3.1. Impact on clinical research staff

Of 31 units, 21 (68%) suffered shortages of on-site staff. The median decrease in personnel across all professional categories was 30% (IQR 0–48) per site. Main causes were institutional contingency policies (58%), COVID-19–infected workers (35%) and redeployment to other hospital areas (7%).

Almost all units (28/31) managed to perform remote data entry, although 23% ($n = 7$) were not adequately equipped for it and reported difficulties performing trial activities from home-based offices.

3.2. Impact on on-site activities performed by sponsors

Most units experienced cancellations of site initiation visits (SIVs) (65%) and monitoring visits (MVs) (87%).

Sixty-seven percent ($n = 35$) of planned SIVs were cancelled, while 29% ($n = 15$) were performed remotely and 4% ($n = 2$) on-site. The decision to postpone visits was taken by sponsors in half of the cases (49%), by institutions (25%) and by sponsors and institutions together (23%).

Sixty-four percent ($n = 196$) of planned MVs were cancelled, whereas 35% ($n = 109$) were performed remotely and 1% ($n = 4$) on-site. The decision to postpone visits was predominantly taken jointly by sponsors and institutions (45%) or by institutions alone (42%).

3.3. Impact on recruitment

The percentage of phase I and phase II trials and molecular platforms that closed to recruitment in at least one site was 48.5% ($n = 16$), 61.3% ($n = 19$) and 64.3% ($n = 9$), respectively.

Eighty-one percent ($n = 25$) of the units halted recruitment of at least one trial or molecular platform from their own portfolio. Five sites (16%) temporarily interrupted recruitment for all active trials and

Table 1
Summary of responses to the survey provided by the 31 early-phase clinical trials units.

Items	Total, n	Total, % ^b		
Baseline data ^a	Phase I trials active, recruiting	33		
	Phase II trials active, recruiting	31		
	Molecular platforms active, recruiting	14		
	Academic-sponsored trials and academic-sponsored molecular platforms actively recruiting	38		
	Industry-sponsored trials actively recruiting	40		
	SIV previously scheduled for March/April 2020	52		
	MV previously scheduled for March/April 2020	309		
	Unit's full-time workers	570		
	Total number of patients recruited in phase I/II studies in 2019	408		
	Total number of patients recruited in molecular platforms in 2019	495		
Impact on personnel	Number of units suffering any kind of shortages of on-site staff	21	68% (21/31)	
	Total reduction in number of on-site workers	170	30% (170/570)	
	Cause of on-site personnel shortage:	59	35% (59/170)	
	- COVID-19—infected workers	98	58% (98/170)	
	- Institutional contingency policy	13	7% (13/170)	
	- Relocation to other hospital areas			
	Units performing remote data entry	28	90% (28/31)	
	Units with appropriate tools for homeworking (e.g remote access to hospital software [VPN])	24	77% (24/31)	
	Impact on on-site activities performed by the sponsors	Units suffering SIV cancellation	20	65% (20/31)
		Number of SIV cancelled	35	67% (35/52)
Postponing SIV decided by:		17	49% (17/35)	
- Sponsor		1	3% (1/35)	
- Investigators		9	25% (9/35)	
- Institution		8	23% (8/35)	
- Sponsor + institution				
Number of SIV performed remotely		15	29% (15/52)	
Number of SIV performed on-site		2	4% (2/52)	
Units suffering MV cancellation		27	87% (27/31)	
Number of MV cancelled		196	64% (196/309)	
Postponing MV decided by:		22	11% (22/196)	
- Sponsor		2	1% (2/196)	
- Investigators		83	42% (83/196)	
- Institution		89	45% (89/196)	
- Sponsor + institution				
Number of MV performed remotely	109	35% (109/309)		
Number of MV performed on-site	4	1% (4/309)		
Impact on recruitment	Units that interrupted recruitment in all trials and molecular platforms	5	16% (5/31)	
	Units that interrupted recruitment in at least one trial	22	71% (22/31)	
	Units that interrupted recruitment in at least one molecular platform ^c	11	45% (11/24)	
	Trials with interrupted recruitment in at least one unit	35	55% (35/64)	
	Trials with interrupted recruitment in at least 50% of the units	17	26% (17/64)	
	Trials with interrupted recruitment in 100% of the units	9	14% (9/64)	
	Molecular platforms with interrupted recruitment in at least one unit	9	64% (9/14)	
	Molecular platforms with interrupted recruitment in at least 50% of the units	7	50% (7/14)	
	Molecular platforms with interrupted recruitment in 100% of the units	5	36% (5/14)	
	New patients recruited to early-phase trials or to molecular platforms ^d	59		
Impact on IMP and research devices	Trials with IMP shortages	0	0%	
	Units shipping IMPs in at least one trial to the patient's home or to the local healthcare institution	18	58% (18/31)	
	Trials in which IMP were shipped to the patient's home or to the local healthcare centres	26		
	Units managing to increase IMP supply to patients	8	26% (8/31)	
	Units suffering shortages of research devices (e.g. sample kits)	3	10% (3/31)	
	Units that experienced difficulties to ship research samples	13	42% (13/31)	
Impact on patient care organisation	Units suffering any kind of limitations in patients' care	15	48% (15/31)	
	Units conducting remote patient visits in other healthcare institutions or by phone	24	77% (24/31)	
	Total number of patient visits conducted:	809	80% (646/809)	
	- Patient visits conducted on-site	646	7% (59/809)	

(continued on next page)

Table 1 (continued)

Items	Total, n	Total, % ^b
- Patient visits conducted in other healthcare facilities	59	13% (104/809)
- Patient visits conducted by phone	104	
Patient visits rescheduled	48	6% (48/809)
Patient visits cancelled	8	
Patients suffering treatment delays	10	
Cause for patients suffering treatment delay:	0	0%
- Not possible to ensure IMP supply	8	80% (8/10)
- Physician's decision	1	10% (1/10)
- Patient/parents' decision	1	10% (1/10)
- Hospital organisational policy		
Patients suffering treatment discontinuation	0	
Units suffering restrictions to perform trial assessments	8	26% (8/31)
Potential patients not being able to be recruited into trials	23	
Alternative provided to patients not being able to be recruited into trials:	4	17% (4/23)
	19	83% (19/23)
- No anticancer treatment		
- Standard-of-care treatment		
Impact on legal aspects	15	48% (15/31)
Units suffering impact in pending contracts (e.g. contracts postponed, or revision of budget delayed)		
Pending contracts postponed	43	
Units procured with sponsor contingency plans for the management of issues related to the COVID-19	29	94% (29/31)
Units developing individual contingency plans for the management of issues related to the COVID-19	29	94% (29/31)
ITCC countries whose National Regulatory Agency developed contingency plans for the management of issues related to COVID-19	10	83% (10/12)
Future perspectives		
Unit Leads recruitment expectations in 2020 compared to 2019:	11	35% (11/31)
- Lower	20	65% (20/31)
- Similar	0	0%
- Higher		
Unit Leads planning changes in organisation over the next months to promote homeworking and remote MVs or SIVs	20	65% (20/31)
Unit Leads that believe that this crisis will make their units better prepared for future crises	31	100% (31/31)

IMP: investigational medical product; ITCC: Innovative Therapies for Children with Cancer consortium.

MV: monitoring visit; SIV: site initiation visit; VPN: virtual private network.

^a Baseline data refer to units' status before 1st March. These are aggregated data from all units.

^b Percentages may not always sum up to 100% due to rounding error.

^c Among the 31 sites, 77% (n = 24) had molecular platforms.

^d Defined by having started trial treatment or having had their tumour profiled.

molecular platforms after institutional decision. Among the other 26 sites, the proportion of industry-sponsored trials and molecular platforms that halted recruitment was 18% against the 9% of academic trials/platforms.

Fifty-nine new patients were enrolled across all units in this period, 61% less than the bimonthly 2019 average (n = 150).

The impact on clinical trial activities, as measured by the rate of studies that were put on hold during that period (Fig. 1), or the relative change in the number of recruited patients compared with that in 2019 (Fig. 2), was heterogeneous across countries.

3.4. Impact on organisation of patient care

All units continued to perform on-site patient visits, but 48% (n = 15) reported limitations in providing best care for patients. Eight units (26%), seven of which were located in mixed adult–paediatric centres, had

restrictions on performing trial assessments due to local strategies (e.g. procedures requiring anaesthesia because of shortage of specialists, fewer slots due to prolonged inter-patient intervals or cancellation of out-patient visits in other disciplines).

Of 809 patient visits performed, 80% were conducted on-site (n = 646), while 13% (n = 104) were conducted by phone and 7% (n = 59) in local hospitals closer to families' home. Only eight patient visits were definitively cancelled.

Among patients being actively treated, 10 experienced treatment delays because of COVID-19–related concerns: physician's decision to guarantee patient's safety (n = 8), hospital organisational policy (n = 1) and parents' fear of COVID-19 (n = 1). No patient on the trial had study discontinuation due to COVID-19.

Twenty-three potentially eligible patients could not be screened for trials because of COVID-19–related constraints. Of those, 83% (n = 19) received other

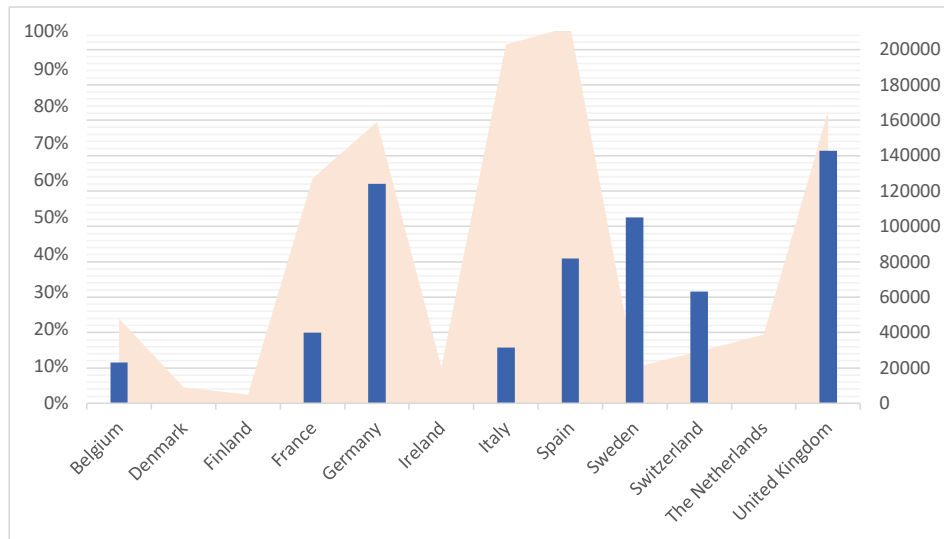


Fig. 1. Overview of COVID-19 diffusion and studies interruption in ITCC countries during the time of the present survey. ■ The percentage of trials and molecular platforms whose recruitment was interrupted per country during the period between 1st of March and 30th April 2020. ■ COVID-19 confirmed infected cases per countries during the period between 1st of March and 30th April 2020. Based on data from the World Health Organization. Coronavirus Disease (COVID-19) Situation Report-137 Highlights Situation in Numbers (by WHO Region); 2020¹.

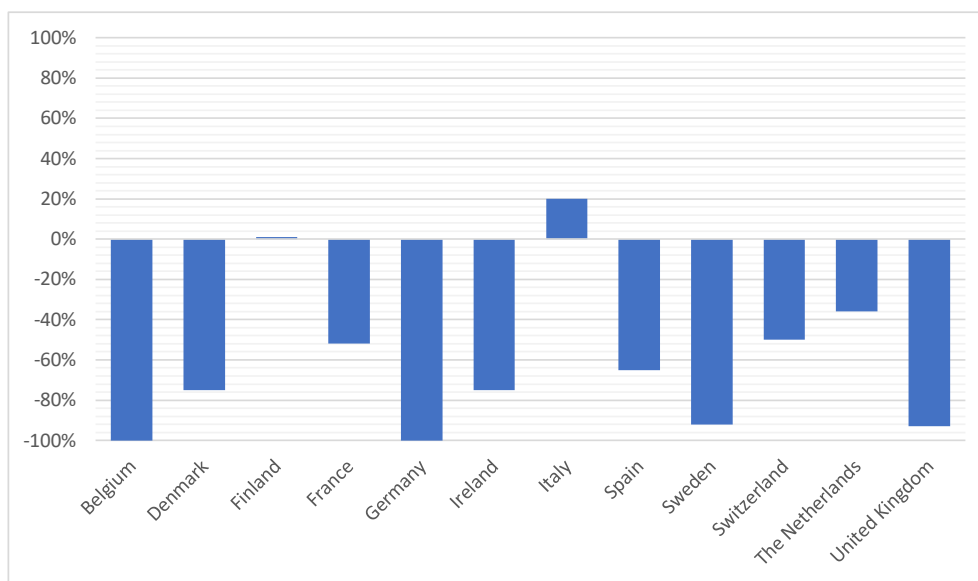


Fig. 2. Relative change in recruitment per country during the period between 1st of March and 30th April 2020 compared with that the 2019 bimonthly mean.

anticancer standard-of-care treatment, and 17% ($n = 4$) did not receive anticancer treatment at that time point.

3.5. Impact on supply of investigational medicinal products and research devices

Provision of IMPs was uniformly maintained at all times. Only three units (10%) suffered research devices shortage (e.g. sample kits). Forty-two percent ($n = 13$) of sites experienced difficulties shipping research samples.

Eighteen units could ship IMPs to patients' homes or local hospitals. In all these cases, the sponsor supported

the shipment of the IMPs. For 16 trials, eight units managed to provide larger amounts of trial medications to patients to minimise hospital visits.

3.6. Impact on administrative and regulatory aspects

Almost half of the units (48%, $n = 15$) suffered impact on administrative and regulatory aspects (e.g. delays in ethics committee submissions, review of trials budget), and the completion of 43 contracts was delayed.

In nearly all units (94%, $n = 29$), local protocols were created, and sponsors procured contingency plans for

the management of COVID-19 issues. National regulatory authorities from 10 of 12 countries surveyed (83%) and developed specific guidance for the conduct of clinical trials during the COVID-19 emergency.

3.7. Future perspective

Sixty-five percent of sites foresee a similar recruitment in 2020 compared with 2019, whereas 35% lower. Most units (65%) are implementing changes to promote remote working and SIVs/MVs.

Fifty-eight percent ($n = 18$) of interviewees responded to the open question about COVID-19–related considerations. Homogenously, they pointed out the proactive attitude from the site staff to develop strategies to minimise potential risks to patient safety and to assure compliance with trial procedures. All investigators agreed that this episode will make units better prepared for future crises.

4. Discussion

This study reveals a profound disruption of paediatric cancer early clinical research due to the COVID-19 pandemic across Europe. Healthcare adjustments were made initially assuming that the pandemic would be brief, but we have come to realise that the pandemic and its consequences are unlikely to dissipate soon. Because children with cancer have an unmet need to access innovative therapies [21], now is the right time to think how to fulfil their needs in this ‘new normal’ setting.

With hospitals diverting resources to care for COVID-19 patients, personnel shortages were a major concern in most units. Physicians and nurses’ activities are patient-centred and therefore more susceptible to be compromised by COVID-19 mitigation measures. Nevertheless, the efforts of healthcare workers to address the issues resulting from this crisis enabled continued care provision for most patients. Other professionals, such as study coordinators or data managers, may continue to perform home-based work more easily. In this regard, most units managed remote data entry, although 23% of them reported to not having the appropriate means to do so. Efforts should be made to implement homeworking solutions under the perspective of COVID-related restrictions expected throughout upcoming months. Although reallocation of staff to other areas to fight against COVID-19 is logical in this context, it has an undeniable impact on areas with highly specialised and multidisciplinary activities, such as clinical research.

Our study shows drastic suspension of SIVs and MVs. The decisions leading to delaying SIVs are understandable because of the inherent complexity of early-phase studies. However, SIVs should be

rescheduled as soon as possible to avoid lost opportunities for patients with no other therapeutic options. In our study, 15 SIVs were performed remotely, demonstrating the feasibility of this procedure. Regarding MVs, only 36% were performed. MVs ensure trial safety and data quality; their suspension may lead to unknown consequences upon the integrity of trials. Hence, it is necessary that sponsors implement alternative mechanisms to resume MVs in collaboration with research teams via reinforced remote communication. Potential impacts of weakening monitoring could be magnified by protocol deviations or delayed visits. Although sponsors provided guidelines to record deviations related to COVID-19 [22,23], regulators should take a sensible approach when reviewing these deviations, especially as most would not compromise patient safety.

More than 50% of the trials and 60% of the molecular platforms interrupted recruitment in at least one unit, and 80% of the sites halted recruitment of at least one trial or molecular platform. The proportion of industry trials stopped is twice the proportion of academic trials, highlighting the key role that academic researchers plays in times of crises and their commitment to cancer patient health over other considerations. Furthermore, patient recruitment during these two months was severely impacted with a 61% drop compared with that in 2019. The reasons for this drop cannot be explained by the halt in trial recruitment alone, but also by individual national lockdown strategies and institutional contingency policies, among others. All efforts should be made to resume recruitment as soon as possible, particularly for phase II trials or molecularly driven studies that have higher chances of success [24].

In an attempt to minimise patient risk, 77% of sites performed remote patient visits in other healthcare institutions or by phone. Although the general population was advised not to visit hospitals because of infection risk, this could constitute a major problem for patients receiving investigational treatments if adverse events do not receive the necessary medical attention or if they suffer treatments delays. Cortiula *et al.* [12] highlighted the negative implications of excessive focus on COVID-19 and of overshadowing other aspects of clinical practice, especially in cancer care.

Fortunately, according to our data, no patient discontinued treatment because of COVID-19. Nevertheless, 23 potentially eligible patients could not be recruited because of COVID-19–related issues. It should be pointed out that whereas COVID-19 has a low mortality rate in children [25], more than 90% of children with relapsed cancers will continue to die. Therefore, considering the safety profile and oral nature of the treatment for most novel anticancer agents, a risk–benefit assessment should be conducted, and cancer treatment continuation should be promoted. Moreover, the stalling process on experimental medicines may extend the already lengthy

marketing process, meaning that some new medicines will take longer to reach the patients across the globe [26].

Several stakeholders are advocating seizing the opportunity to keep the positive clinical trial adaptations implemented during this pandemic permanently [27–29]. Doherty et al. [27] recently suggested changes in trial design and trial implementation so that research units can better cope with future crisis. They include generalisation of virtual visits leaving face-to-face visits for patients and trial monitors only if necessary, administration of medication at home, and efficacy assessments performed closer to patient's home. These suggestions are already in line with some of those raised by the ITCC investigators, and we agree that this is the right time to invest in structural and regulatory changes, so that clinical research is not compromised again to the extent we have seen in this crisis.

Although there are multiple publications about the impact of generic emergency situations in health settings [30,31], there is minimal information that focuses specifically on repercussions on paediatric clinical trials sites [17,18]. The American Society of Clinical Oncology recently published an analysis of the impact of COVID-19 on the conduct of oncology clinical trials [17]. Although focused on the United States research programs in adults, it reports numerous challenges with conducting clinical trials that we have also observed, including enrolment and protocol adherence difficulties or staff constraints.

We acknowledge some limitations of this study. First, its retrospective nature may have limited the accuracy of the data reported, magnified by the fact that during that period site staff were working under unprecedented pressure. Second, some countries were only represented by a fraction of their ITCC sites, therefore potentially limiting the interpretation of individual countries impact. On the other hand, the site coverage, measured by the response rate from the sites, was high (58.5%); 12 of the 14 countries that are part of ITCC were represented, and all sites provided substantially complete responses valid for the analysis; this strengthens the reproducibility and generalisation of the results.

With this study we have identified an extensive disruption in paediatric cancer research during COVID-19 crisis across Europe. We also provided insight into the efforts of sponsors and research teams to maintain access to experimental therapies despite the difficulties. Disruption of ongoing trials wastes time and resources, may reduce patient access to active treatment and carry long-term knock-on effects on drug development. To mitigate the impact, knowledge provided in this study may help reach a consensus strategy for enhancing the adaptability of paediatric clinical trials sites to future crises.

Authors' contributions

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Gilles Vassal: Data acquisition, manuscript editing, manuscript review.

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Francisco Bautista: Study concepts, study design, data analysis, statistical analysis, manuscript preparation, data acquisition, manuscript editing, manuscript review.

Funding

JV was supported by the 2019 ITCC-Fellowship grant. There was no other specific support for this study.

Conflict of interest statement

N. André reports a consulting or advisory role for Bayer, BMS and Akina. He received funding for trial from BMS and molecules for trials from BMS and Pierre Fabre. He received travel support from BMS.

K. Nysom reports a consulting or advisory role for YmAbs and Bayer and receiving honoraria from YmAbs and Bayer.

L. Marshall reports a consulting or advisory role for Bayer, BMS, Eisai and Tesaro and receiving honoraria from Bayer for speaking in symposia/educational events.

M. Gambart reports a consulting or advisory role for Bayer and receiving grants for travel expenses from Jazz pharmaceutical and Eusapharma.

C. Rossig reports receiving honoraria for educational presentations and advice by Amgen, Pfizer, Celgene, Roche, BMS, Novartis and Genentech.

F. Fagioli reports a consultant or advisory role for Amgen, Jazz Pharmaceuticals, Pfizer, Sanofi Genzyme and Takeda.

I. Øra reports a consulting or advisory role for and receiving honoraria from Bayer.

B. De Wilde reports a consultant or advisory role for Bayer, Roche and Novartis.

C. Rizzari reports receiving personal and/or institutional grants, travel support and consultation fees from Amgen, Jazz Pharmaceuticals, SOBI and Servier.

S. Palmu reports a consulting or advisory role for Boehringer Ingelheim and receiving honoraria for educational events and travel expenses from Octapharma and Sobi.

L. Moreno reports being a member of a data monitoring committees for clinical trials sponsored by Novartis, Actuate Therapeutics, Shionogi, Incyte, the University of Southampton and the Royal Marsden NHS Foundation Trust; a consulting role for Novartis and Shionogi. He also reports being a member of the Executive Committee of SIOPEX (European neuroblastoma research cooperative group), organisation which receives royalties for the sales of dinutuximab beta. He reports that his institution receives funding from sponsors for DMC participation, advisory role or conducting industry-sponsored clinical trials.

F. Bautista reports a consultant or advisory role for Bayer, Amgen, Sanofi and EusaPharma and receiving honoraria for speaking at symposia from Amgen and Jazz Pharmaceuticals and support for attending symposia from Takeda, EusaPharma, Shire and Jazz Pharmaceuticals.

The rest of the authors declare that they have no conflict of interest.

Acknowledgements

The authors are grateful to Carole Lecinse, ITCC project manager in Gustave Roussy, for her endless support and help to communicate with each ITCC site.

They are also thankful to all the staff from the ITCC Clinical Trial Units at each site for their invaluable contribution to the advancement of research in paediatric cancer despite this very difficult situation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2020.09.024>.

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