

Papers

Survey on haematopoietic stem cell transplantation for children in Europe

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Summary:

A recent report, prepared in March 2003, regarding the paediatric transplantation activity registered between 1970 and 2002 in the European Bone Marrow Transplantation (EBMT) database showed a decrease in the number of registrations in 2001 and in 2002. In order to validate this observation, the Paediatric Diseases Working Party (PDsWP) secretariat distributed a questionnaire to 395 institutions participating in the EBMT Registry. Each institution was requested to check the number of transplants they reported and to confirm or to correct the figures. As of 15 March 2004, replies had been received from 135 centres reporting a median of 48 transplants per centre over the study period, total 17 891 (58% of the total number). Among them, 55 confirmed their original figures, while 80 corrected the numbers. The overall number of autologous and allogeneic SCTs performed and not reported were 461 and 692, respectively. Most of the teams that corrected their figures stated that their data managers could provide missing data to the EBMT; 260 other teams, each reporting a median of 15 transplants during the study period, total 12 866 (42% of the total number) chose not to reply. A report prepared in March 2004, following the PDsWP survey, showed an increasing number of transplants performed on patients below 18 years of age between 1973 and 2002 and reported to the EBMT Registry (328 autologous and 628 allogeneic) as compared to the 2003 report. This first PDsWP survey, reaching more than 50% of activity in the field, illustrates that the decrease in activity we observed in the 2003 report does not correspond to a decrease in the number of transplants that were actually performed. It demonstrates

the compliance of most major paediatric institutions and confirms the important role of cooperation between National Registries and EBMT Registries.

Bone Marrow Transplantation (2005) 35, S3–S8.

doi:10.1038/sj.bmt.1704834

Keywords: HSCT; children

Haematopoietic stem cell transplantation (SCT) has become a well-established therapy for many severe congenital or acquired disorders of the haematopoietic system, and for chemosensitive, radiosensitive, or immunosensitive malignancies in children and adolescents.^{1–5}

The information deriving from large series of consecutive patients treated in several centres offers an approach for addressing issues in this field and provides a resource for evaluating the changes that have occurred over the last years. With this aim in mind, all EBMT (European Bone Marrow Transplantation Group) members and affiliated nonmembers have reported data on transplanted patients to the EBMT Registry since 1970. A recent report on the paediatric transplantation activity registered between 1970 and 2002 in the EBMT database shows a decrease in the number of SCT registrations in 2001 and in 2002. Moreover, data concerning distribution in the various countries show discrepancies between National Registries and the EBMT Registry.⁶ In order to validate this observation, the Paediatric Diseases Working Party (PDsWP) secretariat distributed a questionnaire on SCT activity to institutions participating in the EBMT Registry. The aim of this paper is to report the preliminary results of this survey and to provide the full picture regarding all children given SCTs between 1970 and 2002.

Design and methods

Data collection is based on the EBMT Registry. In March 2003, the PDsWP secretariat downloaded the number of

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SCTs carried out on patients below 18 years of age that had been reported to the EBMT Registry between 1970 and December 2002. A questionnaire was then distributed to all the EBMT centres involved in this programme. Each institution was requested to check the number of autologous and allogeneic transplants performed within December 2000, as well as in 2001, and in 2002, respectively, and to confirm or to correct the figures immediately. They were asked to supply the number of transplants that were actually performed and to provide missing data to the EBMT Registry directly or through the National Registry.

Each institution was requested to state: if its data manager was able to provide missing data to the EBMT either directly or through the National Registry; if he/she was not able to provide missing data but would appreciate receiving assistance from the EBMT office; and if missing data had already been sent to the EBMT office directly or through the National Registry.

Institutions were classified as: category 1, when they registered children alone; category 2, when more than 25% of registered patients were children; and category 3, when less than 25% of registered patients were children. In order to verify the impact of this survey, the number of SCTs carried out on patients below 18 years of age reported between 1970 and December 2002 were again downloaded in March 2004.

Results

As of March 2003, 30 757 evaluable (18 175 allogeneic and 12 582 autologous) patients aged below 18 years underwent HSCT between 1970 and December 2002 and had been registered by 420 centres in 28 European and 14 extra-European countries. The number of both allogeneic and autologous SCTs per year increased until reaching a maximum of 1447 and 1040, respectively (total 2487) in 1999. After 2000, the number of reported children progressively decreased to a minimum of 1589 (994 allogeneic and 595 autologous) in 2002. Nonetheless, the number of procedures that were reported between 1996 and 2002 was similar to the total number reported over the previous 26 years. Of the 420 centres, 105 performed paediatric transplantation alone (category 1). The remaining 315 centres provided 'combined' programmes (category 2, $n = 25$ and category 3, $n = 290$).

Among the 420 centres, 16 were not reported in the EBMT mailing list and did not receive the questionnaire, despite several efforts to reach them; 319 teams were contacted directly, while 85 institutions from Austria, Czech Republic, Italy, Netherlands, Switzerland, and the United Kingdom received the questionnaires through National Registries. As of 15 March, 2004, 135 centres (60 category 1, 9 category 2, and 66 category 3, reporting 1–1152 transplants in the study period, median 48, total 17 891) had replied to the questionnaire. Among them, 55 confirmed their original figures, while 80 (48 category 1, 5 category 2, and 27 category 3) corrected the numbers. A summary of the transplants reported to the EBMT database and of the transplants that were actually performed by the institutions that answered the question-

naire is reported in Tables 1 and 2. A detailed activity report can be found in the Appendix, in alphabetical order according to country, city, and EBMT centre code. The overall number of autologous and allogeneic SCTs performed and not reported were 498 and 692, respectively. Among the 80 teams that corrected their figures, 65 (43 category 1, 4 category 2, and 18 category 3) stated that their data managers were able to provide missing data to the EBMT either directly or through the national registry; one centre stated that its data manager was not able to provide missing data but would appreciate receiving assistance from the EBMT office; eight stated that missing data had already been sent to the EBMT office directly or through the national registry, the remaining 6 did not answer this question.

Among the 395 teams that were contacted, 260 (38 category 1, 17 category 2, and 205 category 3), reporting 1–1044 transplants in the study period (median 15, total 12 866), for unknown reasons either chose not to reply or simply failed to do so. Among them, 95 centres that each reported 1–335 transplants before 2000 (median 5) did not report any transplants following 2000.

As of March 2004, 31 713 SCTs (18 803 allogeneic and 12 910 autologous) performed between 1970 and December

Table 1 Allogeneic and autologous SCTs by year reported to the EBMT within March 2003, and number of SCTs actually performed from institutions that had replied to the questionnaire

	<i>Reported</i>	<i>Actually performed</i>	<i>Difference</i>
<i>Allogeneic</i>			
1970–2000	8679	9012	333
2001	858	983	125
2002	761	995	234
Total	10 298	10 990	692
<i>Autologous</i>			
1970–2000	6435	6702	267
2001	602	670	68
2002	556	682	126
Total	7593	8054	461
Total SCTs	17 891	19 044	1153

Table 2 Allogeneic and autologous SCTs by category reported to the EBMT, and number of SCTs actually performed from institutions that had replied to the questionnaire

	<i>Reported</i>	<i>Actually performed</i>	<i>Difference</i>
<i>Allogeneic</i>			
Category 1	7574	8084	510
Category 2	1300	1425	125
Category 3	1424	1481	57
Tot allogeneic	10 298	10 990	692
<i>Autologous</i>			
Category 1	6062	6504	442
Category 2	544	565	21
Category 3	987	985	–2
Tot autologous	7593	8054	461
Tot SCTs	17 891	19 044	1153

2002 in patients <18 years of age had been registered and reported by 420 centres in 29 European and 14 extra-European countries.

Discussion

These data reflect the current practice in reporting SCT in childhood in Europe and point to the changes in the number of transplants reported over the last few years. Since 1970, all EBMT members and affiliated nonmembers have collected data concerning transplanted patients. Participating teams are required to register Minimal Essential Data (MED-A) of all consecutive patients. Disease-oriented (MED-B) forms are filled-in by several teams.

The EBMT data managers' job initially involved keeping the data on up to 800 patients provided by 20 centres in an Excel spreadsheet. Today, it extends to 20 000 registrations provided each year by 600 centres through an internet application, with all the complexities that this entails. Since 1990, the EBMT-JACIE (Joint Accreditation Committee International Society for Cell Therapy and EBMT Accreditation Office) initiated an EBMT activity survey, as a rapid tool for quality control and trend assessment.⁷ This activity survey collects numbers of SCT from each participating institution annually, by indication, donor type and stem-cell source, on a single-page questionnaire. During last few years, 465 of 473 member teams returned the survey sheet, corresponding to a 92% return rate.⁸ Unfortunately, it does not provide any information on the age of patients. Since 1995, the PDsWP was set up within the EBMT group⁹ because it became clear that the strategies concerning both SCT and supportive therapy are different in children, adolescents, and adults. Moreover, in paediatrics, one deals with a growing and developing organism with a hopefully long life expectancy. Late effects such as growth retardation, hormonal deregulations, and sterility have a completely different impact from what is observed in adults. As a consequence, it became clear that some characteristics concerning children might be elucidated only through controlled trials restricted to this age group.

Our data show that the decreased activity reported in the 2003 report⁶ did not correspond to a decrease in the number of transplants that were actually performed. This decrease was probably related to the fact that some teams which had previously reported transplants to the EBMT Registry decided to no longer report their data, or encountered problems with the introduction of ProMISE. This hypothesis is confirmed by reports from the activity survey of the Accreditation Committee of the EBMT.⁸

This first PDsWP survey, reaching more than 50% of activity in the field, provides an objective analysis of current practice in reporting data to the EBMT Registry. It illustrates problems that were encountered by several teams, but it shows the willingness to cooperate with most major paediatric institutions: 135 teams, each reporting a median of 48 SCTs had replied to the questionnaire. Among them, 54 confirmed their original figures, while 461 autologous and 692 allogeneic SCTs that had previously

not been reported to the EBMT database were registered with the PDsWP secretariat. Most of these teams stated that their data managers were able to provide missing data to the EBMT either directly or through the national registry.

The report prepared in March 2004, following the PDsWP survey, showed an increase in the number of transplants that were performed on patients below 18 years of age between 1973 and 2002, and that were reported to the EBMT Registry (328 autologous and 628 allogeneic).

This survey contributes to validate the data on paediatric transplants that have been reported to the EBMT registry, and confirms that they may represent a rational basis for health-care planning and patient counselling. That is why reporting data to the EBMT Registry should be considered an essential criterion for the yearly accreditation of EBMT full members. Some questions such as how data quality could be improved, who should be in charge of data validation, and updating can be answered only through a deep cooperation among National Registries, EBMT Registry and Paediatric Diseases Working Party.

Acknowledgements

We acknowledge all the participating teams and the EBMT Registry Subcommittee (C Ruiz de Elvira), the EBMT Acute Leukemia Registry (M Labopin), the Austrian Registry (HT Greinix, B Lindner.), the British Registry (J Apperley, K Towilson), the Czech Registry (M Trnkova, K Benesova), the Dutch Registry (A Hagenbeek, M Smeets), the Italian Paediatric (AIEOP) Registry (A Pession, R Rondelli) and the Swiss Registry (A Gratwohl, H Baldomero). This work was supported in part by a grant from CARIGE and the Compagnia San Paolo.

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Appendix

List of transplant centres that had replied to the questionnaire. The number of allogeneic and autologous transplants reported between 1970 and December 2002 to the EBMT is listed first, followed by the number of allograft and autograft transplants that were actually performed.

*Paediatric centres; #combined centres in which children represented more than 25% of treated patients; °combined centres in which children represented less than 25% of treated patients.

Algeria (1 team; 106-6/106-6)

Alger, Centre Pierre et Marie Curie#, CIC 703, RM Hamladji, (106-6/106-6).

Australia (1 team; 16-0/24-22)

Randwick, Sydney Children's Hospital*, CIC 698, M Vowels, (16-0/24-22)

Austria (7 teams; 402-281/402-280)

Graz, University Children's Hospital*, CIC 593, C Urban (50-40/50-40); Innsbruck, University Hospital°, CIC 271, G Gastl (36-40/36-40); Linz, Elisabethinen-Hospital°, CIC 594, D Lutz (0-5/0-5); Wien, AKH und University°, CIC 227, H Greinix (6-4/6-4); Wien, St Anna Kinderspital*, CIC 528, H Gadner (310-189/310-188); Wien, Hanuschkrankenhaus°, CIC 743, E Koller (0-2/0-2); Wien, Wilhelminenspital°, CIC 828, L Heinz (0-1/0-1).

Belgium (3 teams; 41-30/42-33)

Antwerp, AZ Middelheim°, CIC 783, R Debock (0-4/0-4); Hasselt, Virga Jesse Hospital°, CIC 632 G Bries (0-2/0-2); Liege, University of Liege°, CIC 726, Y Beguin (41-24/42-27).

Czech Republic (1 team; 154-15/172-24)

Prague, University Hospital Motol*, CIC 656, J Stary (154-15/172-24).

Denmark (1 team; 295-56/299-44)

Copenhagen, Pediatric Clinic Rigshospitalet*, CIC 206, C Heilmann (295-56/299-44).

Finland (3 teams; 224-147/247-195)

Helsinki, Hospital for Children & Adolescents*, CIC 219, U Pihkala (205-137/225-177); Helsinki, Helsinki University Central Hospital°, CIC 833, R Janes (0-3/0-3); Turku, Turku University Central Hospital°, CIC 225, K Remes, (19-7/22-15).

France (9 teams; 643-1,719/713-1,703)

Clermont-Ferrand, Hotel Dieu CHU#, CIC 273, F Deméocq (102-243/108-193); Dijon, Hopital d'Enfants CHU de Dijon°, CIC 667, D Caillot (1-9/1-10); Lille, Centre Oscar Lambret#, CIC 972, AS Defachelles (0-52/0-52); Lyon, Hôpital Debrousse*, CIC 806, N Philippe (228-52/285-53); Paris, Hopital Cochin°, CIC 280, F Dreyfus (4-3/4-3); Paris; Hôpital Tenon°, CIC 747, JP Lotz (0-7/0-0); Strasbourg, Hopital de Hautepierre*, CIC 953, B Lioure (79-53/78-64); Vandoeuvre, Hopital d'Enfants*, CIC 676, P Bordigoni (216-161/218-135); Villejuif, Institut Gustave Roussy*, CIC 503, O Hartmann (13-1139/19-1193).

Germany (13 teams; 891-420/1,036-495)

Bremen, Klinikum Bremen-Mitte, CIC 602, CR Meier (0-5/0-5); Dusseldorf, Heinrich-Heine Universität*, CIC 651, U Göbel (145-75/165-87); Giessen, Univ. Children's Hosp.°, CIC 326, A Reiter (7-4/17-9); Hamburg, University Hospital Eppendorf°, CIC 614, AR Zander (113-48/119-48); Ruprecht-Karls Universität°, CIC 524, AM Geueke (1-21/1-13); Jena, Universitäts-Kinderklinik*, CIC 750, F Zintl (130-87/212-148); Magdeburg, Fakultät Otto-von-Schwabing, Klinikum°, CIC 150, N Fischer (6-9/12-3); Rostock, Universität Klinikum°, CIC 585, M Freund (5-2/6-2); Stuttgart, Katharinen Hospital°, CIC 143, J Schleicher (0-3/0-3); Tübingen, University Hospital*, CIC 535, D Niethammer (254-154/263-166); Ulm, Universität Kinderklinik*, CIC 204, W Friedrich (228-10/228-10); Wiesbaden, KMT Zentrum°, CIC 311, R Schwerdtfeger (2-1/13-0).

Greece (1 team; 0-7/0-7)

Athens, Hellenic Cancer Institute St Savas Oncology Hospital°, CIC 751, A Efremidis (0-7/0-7).

Ireland (1 team; 70-1/69-1)

Dublin, St James Hospital Trinity College°, CIC 257, S McCann (70-1/69-1).

Israel (2 teams; 489-133/559-152)

Jerusalem, Hadassah University Hospital#, CIC 258, S Slavin (429-106/499-125); Tel Hashomer, Chaim Sheba Medical Center*, CIC 572, T Amos (60-27/60-27).

Italy (31 teams; 2537-2338/2481-2333)

Ancona, Az. Ospedale Umberto I°, CIC 788, P Leoni (2-21/0-28); Bologna, Università di Bologna*, CIC 790, A Pession (113-168/110-168); Brescia, Università di Brescia*, CIC 741, F Porta (187-41/187-40); Brescia, Spedali Civili°, CIC 288, G Rossi (6-5/6-2); Cagliari, Univ. of Cagliari Osp. per le Microcitemie*, CIC 812, F Argioli (66-13/69-12); Cagliari, PO 'R Binaghi'#, CIC 811, G Lanasa (47-1/47-1); Catania, Divisione Ematologia Pediatrica*, CIC 836, A Di Cataldo (13-20/13-20); Firenze, Azienda Ospedaliera Meyer*, CIC 600, L Faulkner (0-79/3-59); Firenze, Ospedale di Careggi°, CIC 304, A Bosi (25-13/24-12); Genova, Istituto G Gaslini*, CIC 274, G Dini (233-492/234-504); Genova, Ospedale S Martino°, CIC 217, A Bacigalupo (159-40/160-40); Latina, Ospedale S Maria Goretti°, CIC 379, A De Blasio (0-1/0-1); Milano, Istituto Nazionale per

lo Studio e la Cura dei Tumori*, CIC 616, R Luksch (4-177/0-175); Modena, Università di Modena°, CIC 543, F Narni (1-5/1-5); Monza, Ospedale San Gerardo*, CIC 279, C Uderzo (248-51/244-56); Napoli, Ematologia Pediatrica Napoli*, CIC 341, M Ripaldi (22-22/22-21); Padova, Clinica di Oncoematologia Pediatrica*, CIC 285, C Messina (137-190/140-194); Pavia, IRCCS Policlinico San Matteo*, CIC 557, F Locatelli (498-173/502-179); Perugia, Silvestrini Hospital*, CIC 815, A Amici (17-35/23-39); Pescara, Ospedale Civile#, CIC 248, P Di Bartolomeo (198-30/134-5); Pisa, Università di Pisa*, CIC 795, C Favre (68-38/70-39); Ravenna, Ospedale Civile°, CIC 306, G Rosti (0-36/0-36); Roma, Università 'La Sapienza'°, CIC 232, M Vignetti (183-199/183-199); Roma, Ospedale Bambino Gesù*, CIC 315, M Caniglia (19-11/19-12); Roma, Ospedale Bambino Gesù*, CIC 796, G Deb (0-107/0-110); Roma, Università Cattolica S Cuore°, CIC 307, G Leone (2-4/2-4); San Giovanni Rotondo, Ospedale Casa Sollievo della Sofferenza*, CIC 350, M Pastore (0-41/0-42); Torino, Ospedale Regina Margherita*, CIC 305, F Fagioli (153-223/143-233); Torino, Ospedale S Giovanni°, CIC 231, M Falda (7-21/7-21); Trieste, Istituto per l'Infanzia 'Burlo Garofolo'*, CIC 525, M Andolina (122-68/131-68); Verona, Policlinico GB Rossi°, CIC 623, F Benedetti (7-13/7-8).

Netherlands (4 teams; 720-84/698-107)

Amsterdam, Free University Hospital°, CIC 588, GJ Ossenkoppele (1-2/2-3); Leiden, University Hospital*, CIC 203, RM Egeler (583-13/557-33) Nijmegen, St Radboud*, CIC 237, P Hoogerbrugge (49-45/49-45); Utrecht, University Hospital for Children*, CIC 239, M Bierings (87-24/90-26).

Poland (3 teams; 24-52/182-214)

Lublin, Children's University Hospital*, CIC 678, JR Kowalczyk (21-43/29-53); Warsaw, The Medical University of Warsaw°, CIC 954, W Wiktor-Jedrzejczak (2-1/1-1); Wrocław, Wrocław Medical University*, CIC 817, A Chybicka (1-8/152-160).

Portugal (1 team; 64-30/153-99)

Lisboa, Inst. Portugues Oncologia#, CIC 300, M Abecasis (64-30/153-99).

Romania (1 team; 1-0/0-1)

Bucharest, Fundeni University Institute°, CIC 296, C Arion (1-0/0-1).

Russia (2 teams; 31-47/58-56)

St Petersburg, Research Institute of Hematology°, CIC 724, KM Abdulkadirov (6-9/9-10); St Petersburg, Pavlov Medical University#, CIC 725, BV Afanassiev (25-38/49-46).

Slovakia (1 team; 22-25/22-25)

Bratislava, BMT Unit, Pediatric University Hospital*, CIC 684, J Lukac (22-25/22-25).

Slovenia (1 team; 14-8/16-10)

Ljubljana, University Medical Center°, CIC 640, J Pretnar (14-8/16-10).

Spain (13 teams; 725-1103/818-1147)

Barcelona, Hospital Santa Creu i Sant Pau*, CIC 260, I Badell-Serra (126-195/124-198); Barcelona, Hospital Vall d'Hebron*, CIC 527, J Ortega (234-275/322-303); Barcelona, Hospital Universitari Germans Trias i Pujol°, CIC 613, JM Ribera (0-3/0-3); Barcelona, Hospital Sant Joan de Deu*, CIC 668, J Estella (0-46/0-46); Madrid, Niño Jesus Children's Hospital*, CIC 732, M Diaz (103-216/103-216); Madrid, Hospital Infantil La Paz*, CIC 734, AM Martínez-Rubio (72-131/70-134); Madrid, Hospital Gregorio Marañón°, CIC 819, J Diez-Martin (8-11/9-10); Pamplona, Hospital de Navarra°, CIC 577, K Perez (0-7/0-7); Salamanca, Hospital Clínico°, CIC 727, D Caballero (12-15/12-15); Santander, Hospital U. Marqués de Valdecilla°, CIC 242, E Bureo (101-59/101-59); Valencia, Hospital Infantil La Fe*, CIC 653, V Castel (41-131/42-131); Valencia, Hospital Universitario La Fe*, CIC 663, M Sanz (28-12/35-23); Zaragoza, Hospital Clínico°, CIC 531, M Gutierrez (0-2/0-2).

Sweden (4 teams; 448-173/446-175)

Huddinge, Huddinge University Hospital#, CIC 212, P Ljungmann (329-38/329-38); Lund, University Hospital*, CIC 283, A Bekassy (44-58/44-58); Umea, Umea University Hospital°, CIC 731, A Wahlin (2-9/1-10); Uppsala, University Children's Hospital*, CIC 266, J Arvidson (73-68/72-69).

Switzerland (9 teams; 300-162/300-162)

Basel, Basler Kinderspital Abt. Hämato-Onkologie°, CIC 202, A Gratwohl (166-33/166-33); Bellinzona, Ist. Oncol. della Svizzera Italiana °, CIC 829, L Leoncini (0-1/0-1); Bern, University Hospital°, CIC 221, K Leibundgut, M Fey (0-44/0-44); Geneva, Hopital Cantonal Universitarie*, CIC 261, P Wacker (38-16/38-16); Lausanne, Centre Hospitalier Universitaire Vaudois*, CIC 820, M Nenadov-Beck (0-18/0-18); St Gallen, Kantonsspital°, CIC 324, U Hess (0-6/0-6); Zurich, University Hospital°, CIC 208, U Schanz (13-13/13-13); Zurich, University Children's Hospital*, CIC 334, R Seger (81-31/81-31); Zurich, Klinik Im Park°, CIC 700, V Hofmann (2-0/2-0).

Turkey (2 teams; 47-19/48-19)

Ankara, Gülhane Military Medical Academy°, CIC 372, F Arpacı (8-9/8-9); Antalya, Akdeniz University Medical School*, CIC 618, MA Yesilipek (39-10/40-10).

United Kingdom (20 teams; 2,034-737/2,099-744)

Bangor, Ysbyty Gwynedd Hospital°, CIC 736, MH Gilleece (0-1/0-1); Belfast, Belfast City Hospital°, CIC 268, F Jones (4-4/19-3); Birmingham, Heartlands Hospital°, CIC 284, DW Milligan (2-12/2-13); Birmingham, Children's Hospital*, CIC 781, P Darbyshire (267-61/268-60); Bristol, Royal Hospital for Children*, CIC 386, J Cornish (583-93/558-85); Cardiff, University of Wales°, CIC 303, AK Burnett (7-0/7-0); Edinburgh, Western General Hospital°, CIC 228, J Davies (13-4/13-4); Glasgow, Royal Hospital for Sick Children*, CIC 707, B Gibson (87-30/85-31); Leicester, Royal Infirmary°, CIC 713, A Hunter (21-17/23-17); London, Hammersmith

Hospital°, CIC 205, J Apperley (274-9/274-9); London, University College Hospital°, CIC 224, A Goldstone (39-74/44-77); London, Great Ormond Street Hospital*, CIC 243, P Veys (340-172/391-188); Manchester, Christie NHS Trust Hospital°, CIC 780, E Liakopoulou (6-22/6-22); Manchester, Royal Manchester Children's Hospital*, CIC 521, RF Wynn (275-119/282-119); Norwich, The Norfolk

and Norwich University Hospital°, CIC 391, J Parker (0-1/0-1); Nottingham, City Hospital°, CIC 717, N Russell (10-8/10-8); Oxford, Radcliffe Hospital*, CIC 255, T Littlewood (11-36/10-36); Sheffield, Children's Hospital*, CIC 778, A Vora (79-38/85-32); Southampton, General Hospital°, CIC 704, K Orchard (16-35/22-37); Stoke on Trent, North Staffordshire Hospital°, CIC 394, R Chasty (0-1/0-1).