HAUTE AUTORITÉ DE SANTÉ

OPINION OF THE COMMITTEE FOR THE ASSESSMENT OF DEVICES AND HEALTH TECHNOLOGIES

18 April 2007

CONCLUSIONS	
Name:	**CoaguChek XS**, coagulometer for patient self-testing
Models and references concerned:	CoaguChek XS monitor: reference 04625412017 Test strips: boxes of 24 (reference 04625358) and 6 (reference 04625374)
Manufacturer/ Distributor:	**ROCHE DIAGNOSTICS GmbH (Germany) / ROCHE DIAGNOSTICS (France)**
Applicant:	**Coagulation and Thrombosis Study Group (GEHT) and the Paediatric Cardiology Branch (FCP) of the French Society of Cardiology**
Available data:	Only prospective studies specifically carried out in children have been selected. The objectives of these studies are mainly to compare results of self-measurement of International Normalised Ratio (INR) with the coagulometer and with the methods used in laboratories. The number of children included varies from 14 to 93. Seven publications have been selected (including five studies carried out using CoaguChek).
Expected benefit (EB):	**Sufficient,** because of: **- the therapeutic value** of the coagulometer used with children receiving long-term oral anticoagulation therapy (OAT). **- the expected public health benefit,** taking into account the severity of the complications linked to treatment with anticoagulant agents, which are potentially life-threatening.
Indications:	Self-testing of long term oral anticoagulation therapy in children, particularly for: - Children with prosthetic mechanical valves - Cavo-pulmonary shunts - Arterial aneurysms in Kawasaki disease - Pulmonary arterial hypertension - Prevention of intracavity thromboses in cardiomyopathy conditions - Vein or arterial thromboses.
Items affecting the ECB: - Technical specifications: - Procedures for prescription and use:	 No additional requirement in relation to the technical specifications proposed by the manufacturers. CoaguChek XS must only be used by children and their parents who have participated in an educational and training program of anticoagulation management and self-testing.

The prescription of medication, training and follow-up of patients must be carried out by the cardiology or paediatric department in a public or private hospital establishment, specialised in treating children with congenital heart diseases. This department must be trained to manage treatments using anticoagulants, especially in providing therapeutic education and in the use of coagulometer for patient self-testing. The department must also provide a permanent, 24-hour, on-call service.

In children without any cardiological indication, the prescription of medication, training and follow-up of these patients may be carried out by any other department in a public or private hospital establishment, meeting the same requirements as those mentioned above, and when necessary, working in consultation with the specialist organisation specified above.

When the device is prescribed, it must be accompanied by a letter addressed to the treating doctor and the laboratory which will usually carry out the INR checks. Patients and/or their families must be given the details of a person at the hospital they can contact in the event of any problems.

The initial training provided to the child and/or a family member must include:

- The theoretical aspect of anticoagulation and filling in the OAT follow-up diary.
- Practical training in the use of the coagulometer, especially instruction on the finger-prick procedure.

At the end of this training, a check must be carried out by the specialist department, before providing the device, on the actual theoretical and practical knowledge acquired.

This check must verify that the family and/or child has clearly understood the principles behind anticoagulant treatment including: how the coagulometer works, practical training in its usage and in particular, the need for a good quality blood sample, as well as the people to contact in an emergency.

If any aspect of this training is not successful, the trainer must once again go over the information which has not been understood and then re-assess the child’s and/or family’s knowledge.

A continuous assessment of this knowledge, which is required for renewal the prescription for testing strips, must be carried out 12 weeks after the first delivery and repeated every 6 months. This check must be carried out by the department which gave the original training.

The INR results will be sent to the specialist department.

The doctor in the specialist department will adjust the treatment and tell the patient the date of the next check (using coagulometer and/or the conventional laboratory method) and will inform the child’s treating doctor of this.

In the case that an organisation is available to provide training and follow-up for anticoagulation treatment (i.e. an anticoagulation clinic), cooperation must be established with this body (for example by sending a letter with the prescription for the coagulometer and providing the patient and their family with the details of the contacts involved in following up the anticoagulant treatment etc.)

Frequency of tests

The intervals for measuring the INR proposed by the Committee for the Assessment of Devices and Health Technologies (CEPP) are given in the following table:

Weeks	1-3	4-12	12-15	16-27	From 28 onwards
Laboratory INR	1 per week	1 per month			1 per 6 months
Self-testing INR	1 per day	1 per week		1 per 2 weeks	

A check will be carried out using the monitor 48 hours after each change of dosage, after an event likely to modify the INR or in the case of any signs indicating an incorrect adjustment.

Improvement in Expected Benefit (IEB):	**IEB level III (moderate improvement)** in terms of ease of use and the affect on quality of life by using the CoaguChek XS monitor compared with the usual test in laboratory only
Type of registration:	**Brand name**
Duration of inclusion on reimbursement list:	**3 years**
Renewal conditions:	Renewal is subject to the presentation of the results of a clinical study which will include the following criteria: time spent in the target therapeutic range, frequency of checks and number of long-term complications (amount of bleeding and thromboses).
Target population:	According to expert data, the target population of children receiving long-term OAT is estimated at between 500 and 1000, with an estimate of 150 new patients every year.

Definitive opinion 2

Health Technology Assessment Division

EVIDENCE REVIEW

Reason for application

Application for inclusion on the List of Products and Services Qualifying for Reimbursement (LPPR). mentioned in article L 165-1 of social security regulations.

- **Models and references concerned**

CoaguChek XS monitor: reference 04625412017.
Test strips: boxes of 48 (reference 04625315), 24 (reference 04625358) and 6 (reference 04625374).

- **Packaging**

The package contains:
- 1 carrying case
- 1 CoaguChek XS monitor
- 4 x AAA 1.5 V batteries (alkaline manganese)
- 1 lancing device
- 20 lancets

The CoaguChek XS test strips come in packages of 48, 24 and 6, in vials of 24 or 6.

- **Applications**

The application for inclusion on the reimbursement list relates to the following indication:
Self-testing of long-term OAT in children, particularly for:
- Prosthetic mechanical valves
- Cavo-pulmonary shunts
- Arterial aneurysms in Kawasaki disease
- Pulmonary arterial hypertension
- Prevention of intracavity thromboses in cardiomyopathy conditions
- Vein or arterial thromboses.

Reimbursement history

First application for inclusion on the List of Products and Services Qualifying for Reimbursement (LPPR).

Product characteristics and purpose of device

- **CE marking**

CoaguChek XS System (monitor) and CoaguChek XS PT test strips:
In-vitro diagnostic medical device class, notification by Lloyd's Register Quality Assurance (no. 0088), UK, 6 September 2005.

- **Description**

A drop of blood (around 10µL), from a capillary or vein, is applied to the test strip which is outside the monitor. The monitor's operating principle is based on electrochemical measurement (amperometric operation).

The system has a certain number of control functions: checking the electronic components and functions after switching the monitor on, checking the test strip's temperature when taking the measurement,

checking the expiry date and batch information on the test strip, quality control function integrated into the test strip.

Monitor's dimensions: 13.8×7.8×2.8 cm.
Monitor's weight: 175 g (with batteries).
Memory: 100 test results with time and date of measurement.
The INR measuring range is 0.8 to 8.0. The monitor has a 2-year warranty.
The test strips must be kept at a temperature between 18 and 32°C with a relative humidity of 10 to 85%.

- **Intended purpose**

Measuring coagulation based on prothrombin time converted to INR, in order to monitor treatments involving vitamin K inhibitors.

- **Accompanying procedure or service**

Not applicable.

Expected Benefit

1. Value of the device or technology

1.1 Data analysis: evaluation of the therapeutic effect/adverse effects, risks linked to use

Nine publications (seven studies, one meta-analysis, one literature review) released between 1995 and 2006 have been provided in the file.

Only prospective studies specifically carried out in children have been selected.

1.1.1 Non-specific data relating to the device

The study by Massicotte et al.[1] is a prospective study with the aim of evaluating a coagulometer for patient self-monitoring (Biotrack) in children not receiving OAT and in children receiving OAT based on 3 groups (control group: children not receiving OAT before surgery (n=30, mean age of 9 years), group 2: children receiving OAT (n=40, mean age of 14 years), group 3: children receiving OAT in whom laboratory measurement is difficult (n=23, mean age of 3 years)).

The results show that there is no significant difference between the INR measurements taken using Biotrack and those taken using the automated laboratory device for groups 1 and 2, with a significant correlation ($r=-0.93$, $p<0.001$). The INR difference measured using both methods is < 0.8 for 90% of values.

The results for the group self-monitoring at home (group 3) during an average period of 13 months show that the 18 measurements comparing the whole blood monitor INR versus the laboratory INR show no significant difference.

The accuracy of the values (differences in the INR values between Biotrack and the laboratory method) is good for INR values between 2 and 3.5. 90% of the INR results were within 0.8 INR units. Four INR values are below the therapeutic range using the laboratory method and within the therapeutic range with Biotrack. Six INR values are above the therapeutic range using the laboratory method and within the therapeutic range with Biotrack. Out of 599 measurements taken, 63% of INR values taken using Biotrack are within the therapeutic range.

In addition, the patients are satisfied. Only 1 family is discontinuing.

1 Massicotte P, Marzinotto V, Vegh P, Adams M, Andrew M. Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor. J Pediatr. 1995; 389-394.

1.1.2 Data relating to the device

Five studies have been carried out using CoaguChek.

The study by Marzinotto et al.[2] is a prospective study taking place in two phases, with one phase in hospital involving 60 children (aged 3 months to 18 years) and one phase in the patients' home involving 20 children. The purpose is to evaluate the CoaguChek monitor in patients receiving OAT, comparing the self-monitoring INR values with the laboratory INR values (based on two methods) in the hospital (phase 1) and at home (phase 2), with each phase lasting 8 weeks.

The results show a good correlation between the different INR values. The target therapeutic range for the CoaguChek INR differs from the laboratory INR in 29% of cases. The difference measured between both methods is < 0.5 for 71% of values and < 0.9 for 92% of values.

The correlation between the methods carried out in the laboratory is better when the measurement using CoaguChek is taken in hospital rather than at home by the patients themselves or their parents.

The study by Christensen et al.[3] is a prospective study. The aim was to assess the quality of self-management of OAT in children with a congenital cardiac disease. The self-management monitor used is the CoaguChek. The results show that among the 14 children included (mean age of 9.7 years) the target therapeutic range is achieved in 65.5% of cases (from 17.6% to 90.4%). The relative median difference between the INR measured in the laboratory and the INR measured using CoaguChek is 5.3% (p=0.07).

Furthermore, all the patients were able to adjust their dosage of anticoagulants themselves during the performance test carried out in week 27. All the patients, apart from one, also wanted to continue self-management after the one and a half year study period, even though they were responsible for the cost of the device. The only patient who did not want to continue made this decision for financial reasons.

The study by Nowatzke et al.[4] is an analytical study with the aim of comparing the INR measurement of four coagulometers (CoaguChek, Protime Micro-coagulation system, RapidpointCoag, Hemochron Jr. Signature) with an INR measurement taken in the laboratory in children (aged between 22 months and 18 years) receiving OAT (n=19) and whose blood is taken by venepuncture.

The results collected during one year show differences between the INR values measured by the various coagulometers and by using the laboratory method, with the difference varying according to the monitor being examined and therapeutic range. The smallest variations are observed when the INR value measured in the laboratory lies within the therapeutic range between 2 and 3.5.

The study by Ignjatovic et al.[5] is a descriptive study with the aim of determining whether the technique for measuring the INR value using CoaguChek (self-monitoring) and Thrombotest (water bath method) by taking a blood sample by finger-prick is reliable and accurate, compared with an INR analysis carried out by a laboratory (venous sample). Additionally, the study sought to determine whether the INR results obtained for CoaguChek mean that the treatment of children with an oral anticoagulant can be monitored with complete safety guaranteed. The INR tests using Thrombotest and CoaguChek are being carried out by the team.

The results show that among 18 children examined (with a mean age of 11.9 years) and for a period of 6 months, the correlation between CoaguChek and the laboratory method and between Thrombotest and the laboratory method are 0.885 and 0.700 respectively. The mean of the differences is 0.415 between Thrombotest and the laboratory method and 0.138 between CoaguChek and the laboratory method.

2 Marzinotto V, Monagle P, Chan A, Adams M, Massicotte P, Leaker M et al. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and home setting. Pediatr Cardiol. 2000 ; 21:347-352.
3 Christensen TD, Attermann J, Hjortdal VE, Maegaard M, Hasenkam JM. Self-management of oral anticoagulation in children with congenital heart disease. Cardiol Young. 2001; 11: 269-76.
4 Nowatzke WL, Landt M, Smith C, Wilhite T, Canter C, Luchtman-Jones L. Whole blood international normalization ratio measurements in children using near-patient monitors. J Pediatr Hematol Oncol. 2003; 25:33-37.
5 Ignjatovic V, Barnes C, Newall F, Hamilton S, Burgess J, Monagle P. Point of care monitoring of oral anticoagulant therapy in children: comparison of CoaguChek Plus and Thrombotest methods with venous international normalised ratio. Thromb Haemost. 2004; 92: 734-7.

88% of the results for CoaguChek and 57% of the results for Thrombotest have a difference of less than 0.5 INR units, compared to the results obtained using the laboratory method. The INR situation in relation to the therapeutic range (2-3) is different in 25% of cases when the INR is measured with CoaguChek and in 36% of cases when the INR is measured using Thrombotest, compared to the figures for the laboratory method.

The study by Newal et al.[6] is a prospective study with the aim of evaluating the correlation between the results for the tests carried out by parents using a coagulometer (CoaguChek: H-INR) and those carried out by the medical team using the same coagulometer (C-INR), when the parents have gone through an intensive education and training programme.

Over a follow-up period of 26 weeks there is no statistically significant difference between the two mean INR values obtained (the INR measured by the patient at home and the INR measured by the medical team). The INR measured by the patient at home is higher than the INR measured by the medical team in 35.6% of tests, lower in 41.4% of tests and identical in 23% of tests. The correlation is satisfactory (r^2 = 0.949, IC 95%: 0.926 to 0.965, p<0.0001). The therapeutic range is achieved in 65.5% of H-INR tests and 64.4% in C-INR tests.

Parent satisfaction assessed on a scale of 1 to 10 is 9.4.

The literature review by Newall et al.[7] established a list of the various studies carried out on coagulometers in children receiving treatment with oral anticoagulants. Six publications are analysed, including four paediatric studies and two studies involving adults and children. In the four paediatric studies the number of patients included varies from 14 to 60, with children's ages varying from 3 months to 18 years (the two studies including children and adults are less informative in terms of specific paediatric details).

The authors point out that coagulometers offer numerous benefits for children. The results indicate a good level of concordance between the coagulometers and conventional monitoring, and patient satisfaction (using questionnaires). However, they do mention that additional studies need to be carried out.

These studies are summarised in the Appendix.

The studies have shown a good correlation between CoaguChek XS and the measurements taken in a laboratory. However, the Committee emphasises the absence of any studies demonstrating the clinical impact of coagulometer self-testing on children.

1.2 Role in treatment strategy

Currently, the INR is measured in a laboratory using a sample taken by venepuncture from the antecubital fossa.

When the child is stabilised, this test is usually performed twice a month. During the stabilisation phase or a period of intercurrent diseases with other temporary drug treatments, these checks are carried out more often.

Coagulometers for patient self-testing (or self-monitoring) of OAT presents an alternative to taking measurements in a laboratory. However, they do not take the place of this type of measurement completely. Regular checks must be maintained (once a week at the start, then every month during the first six months, then once every six months after that).

At present, two coagulometers have a distributor in France, CoaguChek XS and INRatio. Both monitors play the same role in the therapeutic strategy.

6 Newal F, Monagle P, Johnston L. Home INR monitoring of oral anticoagulant therapy in children using the Coaguchek S point-of-care monitor and a robust education program. Throm Research. 2005.
7 Newall F, Bauman M. Point-of-care antithrombotic monitoring in children. Thromb Res. 2006; 118: 113-21.

In view of the data presented, the CoaguChek XS system provides a benefit for children receiving treatment with an oral anticoagulant for the indications claimed.

2. Expected public health benefit

2.1 Severity of the disease

The long-term use of vitamin K inhibitors for the relevant diseases is associated with a high risk of bleeding or conversely, with life-threatening thrombotic complications
.
The main features of treating children with long term OAT are a greater inter-individual variability in the doses than in adults and the numerous causes of interference (dietary changes, infections etc.). Additionally, taking blood samples is restrictive, painful and difficult to do in children.

2.2 Epidemiology of the disease

A 1998 study carried out in both adults and children by the regional pharmacovigilance centres showed that 13% of hospital admissions for iatrogenic effects were related to bleeding from taking anticoagulant agents. This is equivalent to an average number of 17,000 admissions per year.[8]
We do not currently have any specific data for children.

2.3 Impact

There are no coagulometers included in the List of Products and Services Qualifying for Reimbursement.

The impact of this product on the quality of life of the children and their parents is important (reduction in the number of venous samples, the need to travel, absences from school, needle phobia etc.).

Given the small population of patients, the impact on the healthcare system is slight.

Overall, the Committee for the Assessment of Devices and Health Technologies believes that the Expected Benefit from the CoaguChek XS system is sufficient for inclusion on the reimbursement list for the medical devices and technologies mentioned in article L 165-1 of social security regulations. This inclusion is for children up to the age of 18 years, for the following indications "Self-testing of long-term oral anticoagulation therapy in children, especially for children with prosthetic mechanical valves, cavo-pulmonary shunts, arterial aneurysms in Kawasaki disease, pulmonary arterial hypertension, prevention of intracavity thromboses in cardiomyopathy conditions, vein or arterial thromboses."

8 www.afssaps-sante.fr

Items affecting the Expected Benefit

- Minimum technical specifications

No additional requirement compared with the technical specifications proposed by the manufacturer.

- Procedures for prescription and use

CoaguChek XS must only be used by children and their parents who have received an educational management and training program of anticoagulation and self-testing.

The prescription of medication, as well as the training and follow-up of patients must be carried out by a cardiology or paediatric department in a public or private hospital establishment, which treats children with congenital heart diseases. This department must be trained in the management of anticoagulant treatments, especially in the provision of patient education and in the use of coagulometers for patient self-testing. The department must also provide a permanent 24-hour on-call service.

In children without any cardiological indication, the prescription of medication, coagulometer training and patient follow-up may be carried out by any other department in a public or private hospital establishment, meeting the same requirements as those mentioned above, and when necessary, working in consultation with the specialist organisation specified above.

When the device is prescribed, it must be accompanied by a letter addressed to the primary care physician and the laboratory which will usually carry out the INR checks. Patients and/or their families must be given the details of a person at the hospital they can contact in the event of any problems.

The initial training provided to the child and/or a member of the child's family must include:

- The theoretical aspect of anticoagulation and filling in the OAT follow-up diary.
- Practical training in the use of the coagulometer, especially instruction on the finger-prick procedure.

Upon completion of this training, a check must be carried out by the specialist department, before providing the device, on the actual theoretical and practical knowledge acquired.

This check must verify that the family and/or child has clearly understood the principles behind anticoagulant treatment, including: how the coagulometer works, the practical training in its usage and in particular, the need for a good quality blood sample, as well as the people to contact in an emergency.

If any aspect of this training is not successful, the trainer must once again go over the information which has not been understood and then re-assess the child's and/or the family's knowledge.

A continuous assessment of this knowledge, which is required for renewal the prescription for testing strips, must be carried out 12 weeks after the first delivery and then once every 6 months. This check must be carried out by the department which gave the original training.

The INR results will be sent to the specialist department.

The doctor in the specialist department will adjust the treatment and tell the patient the date of the next check (using coagulometer and/or the conventional laboratory method) and will inform the child's treating doctor of this.

In the case that an organisation is available to provide training and follow-up for anticoagulation treatment, (i.e. an anticoagulation clinic) cooperation must be established with this body (for example by sending a letter with the prescription for the coagulometer and providing the patient and their family with the details of the contacts involved in following up the anticoagulant treatment etc.)

Frequency of tests
The intervals for measuring the INR proposed by the Committee for the Assessment of Devices and Health Technologies (CEPP) are given in the following table:

Weeks	1-3	4-12	12-15	16-27	From 28
INR laboratory	1 per week	1 per month			1 every 6 months
INR self-testing	1 per day	1 per week		1 every 2 weeks	

A check will be carried out using the monitor 48 hours after each dosage adjustment, after an event likely to modify the INR or in the case of any signs indicating an incorrect adjustment.

In view of the fixed test intervals, particularly after week 16, the package of 48 testing strips has not been selected.

Improvement in Expected Benefit

The CEPP has decided in favour of an IEB level III (moderate improvement) in terms of ease of use affecting quality of life using the CoaguChek XS monitor compared with usual laboratory-based testing.

Renewal conditions and duration of inclusion

Renewal conditions:
Renewal is subject to the presentation of the results of a clinical study which will include the following criteria: time spent in the target therapeutic range, frequency of checks and number of long-term complications (amount of bleeding and thromboses).

Proposed duration of inclusion:
3 years

Target population

There are no registers in France or elsewhere in Europe listing the congenital heart diseases from which an estimate of the frequency of the indications for treatment with vitamin K inhibitors could be made.

According to expert data, the number of children receiving long-term treatment with vitamin K inhibitors who have mechanical valves is around 500 patients, while the number presenting with pulmonary arterial hypertension is around 60.

According to expert data, the target population of children receiving long-term OAT is estimated at between 500 and 1000, with an estimate of 150 new patients every year.

APPENDIX: CLINICAL DATA

Reference code / Study name	**Massicotte P, Marzinotto V, Vegh P, Adams M, Andrew M. Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor. J Pediatr. 1995; 389-394**
Study design	Multi-centre, prospective study
Study dates and duration	Not given.
Study objective	Evaluation of whole blood prothrombin time (PT) monitor (Biotrack) when used in healthy children and in consecutive children requiring warfarin therapy.
Devices used	Biotrack (CCD Monitor, Ciba Corning Diagnostic 512 Coagulation Monitor). Monitor not available in France.
METHODS	
Inclusion criteria	Control group (1): INR value measured in hospital Healthy, age-matched subjets who where having routine blood samples taken before scheduled surgery (Ontario). Clinic group (2): INR value measured in hospital Patients requiring warfarin therapy and being followed up through external consultation (Toronto). Home group 3: INR value measured at home Children requiring warfarin therapy in whom it is difficult to have the INR value measured in the laboratory (difficulty accessing the vain, geographical isolation without laboratory services,, monitoring 2-3 times a week to stabilise treatment).
Non-inclusion criteria	/
Study setting and site	Children's Hospital Chedoke-McMaster, Hamilton, Ontario, Canada. Hospital for Sick Children (HSC), Toronto, Ontario, Canada.
Training	Training patients in self-monitoring at home: By the nurse. Parents assessed 3 times before carrying out the test at home. The nurse is in contact with the families every week by telephone and after each home test. The medical team (doctor + nurse) adjusts the treatment according to the INR values. The family is told when to carry out the test and when to call the nurse. If the INR is not within the therapeutic range, the test is repeated and an appropriate clinical decision made. If, after 2 tests, the INR value is > 4.5, the child is taken to hospital immediately to confirm the results using a conventional test method. Taking samples and determining the prothrombin times and INR values: All the patients in groups 1 and 2, and some patients in group 3 automatically have a venous sample taken to determine the PT and INR values using the conventional laboratory method (reagent: Thromborel S). All the patients (groups 1, 2 and 3) have their values measured using Biotrack. The target INR values cover 3 therapeutic ranges depending on whether the treatment is curative (INR: 2-3), prophylactic (1.4-1.9) or prophylactic where the patient has a prosthetic valve (2.5-3.5).
Primary endpoint	No clearly defined endpoint.
Secondary endpoint(s)	Comparison of haematocrits. Comparison of prothrombin times (PT) and INR values. Patient satisfaction (method not specified).
Sample size	Number of subjects required: not calculated.
Duration of follow-up	The average duration for using Biotrack is 13 months (2-60 months).
Method of randomisation	Not randomised.
Statistical analysis	Linear regression for the correlation between the Biotrack INR and reference laboratory INR values. The mean values between the different groups are compared using a Student's t-test with

<table>
<tr><td></td><td>Bonferroni correction for multiple measurements.</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Number of subjects analysed</td><td>93 children:</td></tr>
<tr><td>Patient characteristics and comparability of groups</td><td>Control group (1): 30 children, mean age of 9 years (1-16).

Clinic group (2): 40 children, mean age of 14 years (1-18). 24 patients have a congenital heart disease, including 13 who have received a prosthetic valve. 16 have deep-vein thrombosis with a pulmonary embolism (DVT+PE).

Home group (3): 23 children, mean age of 3 years (5 months-14 years). 13 have a congenital heart disease, including 4 with a prosthetic valve; 10 have a DVT+PE and one suffered a cerebral vascular accident.</td></tr>
<tr><td>Results for primary endpoint</td><td>/</td></tr>
<tr><td>Results for secondary endpoint(s)</td><td><u>PT and INR comparison between the laboratory and Biotrack analyses (groups 1 and 2)</u>

<table>
<tr><td></td><td>Group 1
N=30</td><td>Group 2
N=40</td></tr>
<tr><td>Haematocrit</td><td>0.38±0.022</td><td>0.41±0.70</td></tr>
<tr><td>Prothrombin time (PT):
Laboratory
Biotrack
Significance (p)</td><td>
11.2±0.69
12.0±0.90
NS</td><td>
27.0±1.40
18.8±0.43
p<0.01</td></tr>
<tr><td>INR:
Laboratory
Biotrack
Significance (p)</td><td>
1.0±0.07
1.0±0.14
NS</td><td>
2.7±0.15
2.6±0.10
NS</td></tr>
</table>

The correlation of the INR values between the 2 methods is significant (r = 0.93, p<0.001) for all the patients in both groups.

The Biotrack’s accuracy is evaluated via a graph representing the value of the Biotrack INR versus conventional INR, as a function of the conventional INR. The INR difference measured using both methods is < 0.8 for 90% of values. 10 discrepancies could have consequences for the therapeutic approach: 4 INR values are below the therapeutic range using the conventional method and within the therapeutic range with Biotrack. 6 INR values are above the therapeutic range using the conventional method and within the therapeutic range with Biotrack.

<u>Self-monitoring at home (group 3):</u>
The 18 measurements comparing the whole blood monitor INR versus the laboratory INR show no significant difference.

The accuracy of the values (differences in the INR values between Biotrack and the laboratory) is good for INR values between 2 and 3.5. 90% of the INR results were within 0.8 INR units. 4 INR values are below the therapeutic range using the conventional method and within the therapeutic range with Biotrack. 6 INR values are above the therapeutic range using the conventional method and within the therapeutic range with Biotrack.

Out of 599 measurements taken, 63% of INR values measured using Biotrack are within the therapeutic range.

Mean of 3 measurements per month (1 to 11 months). Mean of 1.8 dose adjustments per month (1 to 4.5).

<u>Parent and child satisfaction (group 3)</u>:
1 family is discontinuing.
Out of 22 patients 2 died from their disease and 6 patients are discontinuing treatment. The remaining 14 patients have continued monitoring using Biotrack without any problem.</td></tr>
</table>

Side-effects	Complications: (group 3) 1 subdural haemorrhage (INR of 4.1, above the therapeutic range for less than 24 hours) and 1 new thrombus (INR of 1.2, below the therapeutic range (1.3 to 1.9) for less than 2 days). Both problems have been resolved without any sequelae.

Reference code / Study name	**Marzinotto V, Monagle P, Chan A, Adams M, Massicotte P, Leaker M et al. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and home setting. Pediatr Cardiol. 2000; 21:347-352.**
Study design	Multi-centre, open-label prospective study.
Study dates and duration	Not given.
Study objective	Evaluating CoaguChek in patients receiving treatment with an oral anticoagulant according to 2 phases, in hospital and at home.
Devices used	CoaguChek (Roche Diagnostics).
METHODS	
Inclusion criteria (Eligibility criterion)	Phase 1: hospital phase Children (< 18 years) receiving treatment with an oral anticoagulant. Phase 2: home phase Same population as for phase 1. However, the children are followed up at home. The parents must fulfil the following criteria: - they can understand the instructions. - they are prepared to carry out the test at home, with confirmation tests in the laboratory for the duration of the study (2 checks carried out in the first week, 1 in week 4 and 1 in week 8, carried out on the same day). - they are able to adequately perform finger-pricks to obtain blood sample. - they are able to operate the CoaguChek monitor.
Non-inclusion criteria	/
Study setting and site	Hospital for Sick Children (HSC), Toronto, Ontario, Canada. Hamilton Civic Hospital's Research Centre (HCHRC), Hamilton, Ontario, Canada.
Training	Training given by the nurse who introduces the study and the requirements, demonstrates how to use the coaguchek monitor and gives instructions on the finger-prick procedure. Parents and children assessed before carrying out the test at home. Parents and children are taught to check the equipment every time they open a box if the INR results are abnormal and they think that there was a problem with the storage of the test strips. The families must record in a follow-up notebook the INR values and any adjustment to the coumadin dose. Monitoring must take place at least every week, or more often if clinically indicated. The target INR values cover 3 therapeutic ranges depending on whether the treatment is curative (INR: 2-3), prophylactic (1.4-1.9) or prophylactic where the patient has a prosthetic valve (2.5-3.5). The nurse is in contact with the families every week by telephone and after each home test (H-INR). Taking samples and determining the INR values: The INR measurements in the laboratory are obtained by venepuncture. A measurement is taken at the HSC using an Electra 1400 (MLA) automated device. Another conventional measurement is taken at the Hamilton hospital using an IL (Instrument Laboratory) automated device with the reagent Thromborel S (Behring Diagnostics). The INR measurements taken using CoaguChek are carried out based on a capillary blood sample (by finger-prick). It is not indicated who performs the treatment adjustments. Questionnaires are completed by the family during phase 2 concerning the training programme, use of CoaguChek, the user manual, storage and control.

<table>
<tr><td>Primary endpoint</td><td>No clearly defined endpoint.</td></tr>
<tr><td>Secondary endpoint(s)</td><td>Comparison of the INR value and prothrombin time (PT) between the 3 methods (CoaguChek and 2 conventional laboratory analysis methods).
Patient satisfaction (questionnaires).</td></tr>
<tr><td>Sample size</td><td>Number of subjects required: not calculated.</td></tr>
<tr><td>Duration of follow-up</td><td>Each phase lasts 8 weeks.</td></tr>
<tr><td>Method of randomisation</td><td>Not randomised.</td></tr>
<tr><td>Statistical analysis</td><td>The correlation between the measurements taken using CoaguChek and the conventional tests is analysed using linear regression. The results for phases 1 and 2 have been analysed separately. An ANOVA test is used to compare the values obtained using the 3 methods. A Student’s t-test with Bonferroni correction is used to analyse the differences.</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Number of subjects analysed</td><td>80 patients.
60 children for phase 1, 20 children for phase 2.</td></tr>
<tr><td>Patient characteristics and comparability of groups</td><td>Ages: 3 months to 18 years.
29% of the children have a prosthetic heart valve, 27% have a congenital heart disease, 8% have a deep-vein thrombosis, 8% have a nephrotic syndrome and 18% have a spectrum of other diseases.</td></tr>
<tr><td>Results for primary endpoint</td><td>/</td></tr>
<tr><td>Results for secondary endpoint(s)</td><td>The average number of INRs performed per month ranged from 9.5 in children under 1 year old and 4.3 for children ages 11 to 18 years. The average number of changes in warfarin dose per month ranged from 4.5 for children under 1 year to 1.8 for children aged 11 to 18 years. There is no information for children between 1 and 11 years.

<u>PT and INR comparison between the laboratory (conventional tests) and CoaguChek analyses</u>

<table>
<tr><td></td><td>CoaguChek</td><td>HSC (laboratory)</td><td>HCHRC (laboratory)</td></tr>
<tr><td>Patients in phase 1:
Average (95% CI) PT (sec)
Average (95% CI) INR</td><td>
17* (16.6-18.7) [a]
2.2 (2.0-2.6) [b]</td><td>
16* (15.4-17.4) [a]
1.9 (1.6-2.1) [b]</td><td>
22 (19.9-24.7)
2.0 (1.8-2.3)</td></tr>
<tr><td>Patients in phase 2:
Average (95% CI) PT (sec)
Average (95% CI) INR</td><td>
18* (17.2-19.2) [a]
2.4 (2.1-2.6) [b]</td><td>
18* (17.5-19.3) [a]
2.3 (2.1-2.4) [b]</td><td>
24 (22.6-26.2)
2.3 (2.1-2.4)</td></tr>
</table>
[a] Comparison of PTs between CoaguChek and HCHRC and between HSC and HCHRC
[b] Comparison of INRs between CoaguChek and HCHRC and between HSC and HCHRC
* p<0.001

In the case of the prothrombin time (PT), the differences are statistically significant between the 3 methods (p<0.001), which reflects the thromboplastin differences. On the other hand, the INR values are not statistically different in these 3 groups. The correlation of the INR values between the 2 conventional methods is significant (r = 0.95), for either phase 1 or phase 2. The INR values measured by CoaguChek in phase 1 are well correlated with the INR values measured using the other two methods (r=0.96 and r=0.92). The correlation between the CoaguChek INR values measured at home in phase 2 is slightly less good in relation to the other two methods (r=0.76 and r=0.74).

The CoaguChek INR differs from the conventional INR (HSC) therapeutic range in 29% of cases.

The difference between the INR measured using CoaguChek and that measured at the HSC</td></tr>
</table>

	is < 0.5 for 71% of the values and < 0.9 for 92% of the values. The results are identical when the CoaguChek INR values are compared with the other method (HCHRC). There is no correlation between the increase in the INR value and delta INR. Questionnaire results All the patients feel that the training helped them and that they do not require any additional information. Additionally, they feel that CoaguChek is easy to use and preferable to venepuncture INRs.
Side-effects	No difference in terms of thrombotic and bleeding complications between the patients treated at the clinic and the patients treated at home.

<table>
<tr><td>Reference code / Study name</td><td>Christensen TD, Attermann J, Hjortdal VE, Maegaard M, Hasenkam JM. Self-management of oral anticoagulation in children with congenital heart disease. Cardiol Young. 2001; 11: 269-76.</td></tr>
<tr><td>Study design</td><td>Single-centre, prospective study</td></tr>
<tr><td>Study dates and duration</td><td>The inclusions started in November 1997 and ended in January 1999.</td></tr>
<tr><td>Study objective</td><td>Evaluating the quality of self-management of oral anticoagulation in children with a congenital cardiac disease.</td></tr>
<tr><td>Devices used</td><td>CoaguChek coagulometer (Roche Diagnostics).</td></tr>
<tr><td colspan="2">METHODS</td></tr>
<tr><td>Inclusion criteria</td><td>Age between 0 and 6 years.
Interest in self-management of oral anticoagulation, with good compliance evaluated according to the interviews carried out with the patients and their parents.</td></tr>
<tr><td>Non-inclusion criteria</td><td>Coagulopathy.
Hepatic disease.</td></tr>
<tr><td>Study setting and site</td><td>Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Denmark.</td></tr>
<tr><td>Protocol</td><td>The patients and their parents have been trained in the use of CoaguChek (the details of this training are not given).

The venous blood samples for the checks are taken either at the hospital where the patients are being followed up or in another hospital laboratory close to the patients' homes. Each patient must always be followed up in the same hospital laboratory.

<u>Frequency of tests</u>
<table>
<tr><td>Weeks</td><td>1 to 3</td><td>4 to 15</td><td>16 to 27</td><td>28 to 51</td></tr>
<tr><td>Laboratory INR</td><td>1 per week</td><td>1 every 3 weeks</td><td>1 per month</td><td>None</td></tr>
<tr><td>CoaguChek INR</td><td>1 per day</td><td colspan="3">1 per week</td></tr>
<tr><td>CoaguChek control by the patient (with control solution)</td><td colspan="4">1 per month</td></tr>
<tr><td>CoaguChek control by the hospital</td><td colspan="4">1 every 6 months</td></tr>
<tr><td>Events</td><td>The doctor adjusts the doses</td><td>Patients suggest the doses and the doctor approves</td><td>Patients adjust their treatment and the doctor checks every 2 weeks</td><td>Patients adjust their treatment and send their data every 12 weeks</td></tr>
<tr><td>Duration</td><td>3 weeks</td><td>12 weeks</td><td>12 weeks</td><td>24 weeks</td></tr>
</table>
In week 27 the patients demonstrate their knowledge through a multiple choice performance test.</td></tr>
<tr><td>Primary endpoint</td><td>No clearly defined endpoint.</td></tr>
<tr><td>Secondary endpoint(s)</td><td>Percentage of time spent in the therapeutic range.
Thromboembolic events and haemorrhagic complications.
Families' satisfaction.</td></tr>
<tr><td>Sample size</td><td>Number of subjects required: not calculated.</td></tr>
<tr><td>Duration of follow-up</td><td>The overall mean period of observation is 547 days (from 214 to 953 days).</td></tr>
</table>

Method of randomisation	Randomisation of patients was initially planned for conventional management or self-management for 6 months, followed by an additional 1 year of self-management for all patients. As the number of patients was too small, randomisation was not carried out.
Statistical analysis	The statistical analysis was carried out using SAS, a statistical software package (version 6.12). The results from self-management and conventional measurements taken in the laboratory were analysed, apart from the measurements from the first 25 days of the study, which was the period for learning how to use the monitor.
RESULTS	
Number of subjects analysed	14 patients included 13 patients analysed (1 patient died).
Patient characteristics and comparability of groups	Mean age of 9.7 years (2.2 to 15.6 years) The INR target therapeutic range was defined for each patient (12 patients have a therapeutic range between 2 and 3, while 2 patients have a range between 2.5 and 3.5). Two coumarins were used (phenprocoumon and warfarin).
Results for primary endpoint	/
Results for secondary endpoint(s)	The therapeutic range is achieved in 65.5% of cases (from 17.6% to 90.4%). The relative median difference between the INR measured in the laboratory and the INR measured using CoaguChek is 5.3% (p=0.07). The total number of INR measurements taken was 801, with an average of 57 measurements per patient (17-118), counted from week 18 of the study. All the patients were able to adjust their anticoagulant dosage themselves during the performance test carried out in week 27. All the patients were satisfied. Only 1 patient did not wish to continue self-management (for financial reasons) after the one and a half year study period.
Side-effects	No patients developed thromboembolic or major haemorrhagic events. 1 patient developed subcutaneous haematomas.

<table>
<tr><td>Reference code / Study name</td><td>Nowatzke WL, Landt M, Smith C, Wilhite T, Canter C, Luchtman-Jones L. Whole blood international normalization ratio measurements in children using near-patient monitors. J Pediatr Hematol Oncol. 2003; 25:33-37.</td></tr>
<tr><td>Study design</td><td>Analytical study.</td></tr>
<tr><td>Study dates and duration</td><td>Not given.</td></tr>
<tr><td>Study aims</td><td>Comparison of the measurement of 4 INR coagulometers with a measurement taken in a laboratory according to the CA-1000 method (“reference” method) in children.</td></tr>
<tr><td>Devices used</td><td>CoaguChek (Roche Diagnostics).
Protime Micro-coagulation system (International Technidyne Corp.).
RapidpointCoag (Bayer Diagnostics).
Hemochron Jr.Signature (International Technidyne).</td></tr>
<tr><td colspan="2">METHODS</td></tr>
<tr><td>Inclusion criteria</td><td>Children treated with an oral anticoagulant.
All the patients received the same dose of warfarin (Coumadin) for at least 7 days.</td></tr>
<tr><td>Non-inclusion criteria</td><td>/</td></tr>
<tr><td>Study setting and site</td><td>Saint Louis Hospital and the paediatric clinic at Washington University Medical School, St Louis Missouri USA.</td></tr>
<tr><td>Training</td><td>Not applicable</td></tr>
<tr><td>Sample collection</td><td>The samples are all obtained via venepuncture (and not via finger-prick) for the self-monitoring devices.
Venous blood is collected by people experienced at taking samples in a syringe.
The INR value is measured by the conventional method using CA 1000 (Sysmex).</td></tr>
<tr><td>Primary endpoint</td><td>No clearly defined endpoint.</td></tr>
<tr><td>Secondary endpoint(s)</td><td>- Assessment of the correlation.
- Assessment of the accuracy carried out in two healthy volunteers.</td></tr>
<tr><td>Sample size</td><td>Number of subjects required: not calculated.</td></tr>
<tr><td>Duration of follow-up</td><td>Not applicable</td></tr>
<tr><td>Method of randomisation</td><td>Not randomised.</td></tr>
<tr><td>Statistical analysis</td><td>Linear regression for assessing the correlation.</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Number of subjects analysed</td><td>19 patients during a total of 30 visits.</td></tr>
<tr><td>Patient characteristics and comparability of groups</td><td>Patients between 22 months and 18 years.
The INR target therapeutic range is given by the doctor.

<table>
<tr><td>Characteristics</td><td>Observation at each visit
N=30 visits</td></tr>
<tr><td>Age (years):
Median
Minimum
Maximum</td><td>
14
2
18</td></tr>
<tr><td>INR</td><td>2.0-3.5</td></tr>
<tr><td>Diagnosis:
Congenital heart disease
Artificial heart valve
Thrombosis
Cardiomyopathy</td><td>
12
12
6
2</td></tr>
</table>
</td></tr>
</table>

Results for primary endpoint	/
Results for secondary endpoint(s)	The results were collected for a period of a year. <u>Comparison of linear regressions for the 4 devices versus the reference analysis (CA-1000)</u> The INR values measured vary between 1.05 and 5.25. The differences in the reference analysis vary between -43.1% and 69.9%. When the INR value measured using the conventional method is < 2, the INR value from the monitor is most often overestimated. Out of 16 INR results < 2 obtained using the conventional method, the INR values obtained using the monitor differ by over 20% in relation to the INR value obtained using the conventional method in 50% (32/64) of cases. The correlation is better when the INR value obtained using the conventional method lies in the therapeutic range (2-3.5). For INR values > 3.5 obtained using the conventional method, 29% (7/24) of the INR values obtained using the devices differ by over 20% in relation to the INR value obtained using the conventional method, with the INR value obtained using the monitor most often lower than the INR obtained using the conventional method.

Device	r^2	Gradient	n
CoaguChek	0.877	0.84	30
Hemochron Jr.	0.834	0.57	30
Protime	0.885	0.70	30
RapidpointCoag	0.923	0.89	30

<u>Assessment of the accuracy</u>
The assessment of the accuracy was carried out in two healthy volunteers.

One volunteer received an anticoagulant treatment (4.7 mg/day). The other volunteer did not receive any treatment. The adult volunteers have samples taken in the same conditions.

The procedure was repeated 10 times in the volunteer treated with warfarin and 16 times in the volunteer who received no treatment.

	No treatment			Treatment with anticoagulant		
	Mean	Standard deviation	% CV	Mean	Standard deviation	% CV
CA-1000	0.91	0.02	2.7	2.32	0.08	3.6
CoaguChek	1.04	0.05	4.9	2.37	0.19	8.0
Hemochron Jr.	1.05	0.07	7.0	2.17	0.30	13.9
Protime	1.03	0.08	7.4	2.51	0.13	5.0
RapidpointCoag	0.91	0.20	22.3	2.42	0.35	14.4

The venepuncture sampling method is not the recommended method for the use of self-monitoring coagulometers.

Side-effects	Not given.

Reference code / Study name	**Ignjatovic V, Barnes C, Newall F, Hamilton S, Burgess J, Monagle P. Point of care monitoring of oral anticoagulant therapy in children: comparison of CoaguChek Plus and Thrombotest methods with venous international normalised ratio. Thromb Haemost. 2004; 92: 734-7.**
Study design	Single-centre, descriptive study
Study dates and duration	Not given.
Study aims	To determine whether: - the method for measuring the INR value using CoaguChek and Thrombotest (sample from the finger) is reliable and accurate, compared with the analysis of an INR value taken by a laboratory (venous sample). - the INR results obtained using CoaguChek can provide a safe method for the follow-up of oral anticoagulation treatment of children.
Devices used	CoaguChek (Plus).
METHODS	
Inclusion criteria	Patients treated with warfarin.
Non-inclusion criteria	/
Study setting and site	Royal Children's Hospital (RCH) in Melbourne, Victoria, Australia.
Sample collection	<u>Taking samples and determining the prothrombin times and INR values</u> The INR value for patients is determined according to 3 procedures. They have 2 capillary blood samples taken to determine the INR value using CoaguChek and Thrombotest (finger sample) and a venous sample for determining the INR value using the conventional laboratory method. Thrombotest is the test usually used at the RCH. This method involves the use of a water bath (37°C) using a sample of total blood taken from a capillary. The laboratory test is carried out using ACL 100 (Instrumentation laboratory) based on a venous sample. The INR tests using Thrombotest and CoaguChek are being carried out by the team. The team using Thrombotest is doing so blind, which means that they do not know the INR results taken using CoaguChek. All the clinical decisions are made based on the Thrombotest results.
Primary endpoint	No clearly defined endpoint.
Secondary endpoint(s)	- Assessment of the correlation. - Comparison of the mean INR values.
Sample size	Number of subjects required: not calculated.
Duration of follow-up	6 months.
Method of randomisation	Not randomised.
Statistical analysis	The correlation between the INR values measured using the 3 methods is calculated by Lin's concordance coefficient, along with a Bland-Altman analysis in order to investigate the average of the differences between the methods. Data analysis via STATA, release 7.
RESULTS	
Number of subjects analysed	18 children

<table>
<tr><td>Patient characteristics and comparability of groups</td><td>Age between 9 months and 21 years (mean: 11.9, SD: 5.03 years).</td></tr>
<tr><td>Results for primary endpoint</td><td>/</td></tr>
<tr><td>Results for secondary endpoint(s)</td><td>40 tests were carried out over a period of 6 months.

<u>INR values obtained from a capillary sample (CoaguChek and Thrombotest) and from a venous blood sample:</u>

<table>
<tr><td>Test</td><td>INR value
Mean (95% CI)</td></tr>
<tr><td>Laboratory INR
Thrombotest
CoaguChek</td><td>2.09 (1.92-2.26)
2.63 (2.36-2.91)
2.25 (2.05-2.45)</td></tr>
</table>
Thrombotest versus venous INR: P=0.0014.
CoaguChek versus venous INR: P=0.2292.

The correlation between CoaguChek and the conventional method and the correlation between Thrombotest and the conventional method are 0.885 and 0.700 respectively. The average of the differences is 0.415 between Thrombotest and the conventional method and 0.138 between CoaguChek and the conventional method.

88% of the results for CoaguChek and 57% of the results for Thrombotest have a difference of less than 0.5 INR units, compared to the results obtained using the conventional method.

The INR status in relation to the therapeutic range (2-3) is different in 25% of cases when the INR is measured with CoaguChek and in 36% of cases when the INR is measured using Thrombotest, compared to the figures for the conventional method.</td></tr>
<tr><td>Side-effects</td><td>No thrombotic or haemorrhagic complications during the study period.</td></tr>
</table>

Reference code / Study name	**Newal F, Monagle P, Johnston L. Home INR monitoring of oral anticoagulant therapy in children using the Coaguchek S point-of-care monitor and a robust education program. Throm Research. 2005.**
Study design	Single-centre, prospective study
Study dates and duration	Not given.
Study objective	Evaluating the correlation between the results of tests carried out using CoaguChek by parents (H-INR) and those carried out by the medical team (C-INR). The parents followed an intensive education and training programme (PRECEDE).
Devices used	CoaguChek S Monitor (Roche).
METHODS	
Inclusion criteria	Parents of the children receiving long-term treatment with warfarin who agree to follow the training programme before carrying out the INR tests at home.
Non-inclusion criteria	/
Study setting and site	Haematology Department at the Royal Children's Hospital (RCH) in Melbourne, Victoria, Australia.
Training	Intensive education and training programme for parents: Predisposing Reinforcing and Enabling Causes in Educational Diagnosis and Evaluation (PRECEDE). This programme includes specific training on the CoaguChek monitor (how to use and maintain the device for carrying out INR tests) and on warfarin (action mechanism, adverse effects, complications and reaction time, factors influencing the therapeutic balance) with theory and practical tests. 2 half-day group training sessions and 2 individual sessions are carried out. Theory assessment using a questionnaire (12 questions): the percentage of correct answers must be > 75%. Practical assessment in the form of carrying out an INR test accurately with the main investigator. If parents fail the theory and/or practical assessments they must attend the training sessions again until they have passed both evaluations. Carrying out the H-INR test: The parents carry out the H-INR at home; call the main investigator (MI), who indicates when to carry out the next test. This test is carried out by the parents and medical team at the RCH for the control evaluation (C-INR). The C-INR is carried out by the medical team using their standard method (CoaguChek). If the difference between the 2 tests is acceptable ($\leq \pm$ 0.2 INR units), the parents return home, redo the next H-INR alone, then call the main investigator etc. If the difference is not acceptable ($> \pm$ 0.2 INR units), the results from the C-INR are the ones accepted and the following test (H-INR) must again be verified at the RCH (C-INR).
Primary endpoint	No clearly defined endpoint.
Secondary endpoint(s)	Evaluating the correlation between the INR data obtained at home (Home INR (H-INR)) and the INR results obtained at the hospital (Control INR (C-INR)). Theoretical evaluation of knowledge. Descriptive elements about how the study has been carried out (average number of contacts with the coordinator, average interval between the INR tests, average number of combined H-INR and C-INR tests etc.). Parent satisfaction assessed on a scale of 1 to 10, carried out at the end of the study.

	Evaluation of side-effects.
Sample size	Number of subjects required: not calculated.
Duration of follow-up	26 weeks.
Method of randomisation	Not randomised.
Statistical analysis	Theoretical assessment of knowledge: Comparison (before-after) of average scores, t-test using STATA. Assessment of how the H-INR test is carried out: Averages and/or median values (SD (Standard Deviation), 95% CI) using STATA. Correlation between H-INR and C-INR: Lin's correlation coefficient. Bland and Altman analyses. Assessment of side-effects: Secondary events include all the thrombotic episodes and major bleeding incidents. Major bleeding incidents are defined as incidents requiring a red blood cell transfusion, hospital admission or a drop in haemoglobin $\geq$ 2 g/L.
RESULTS	
Number of subjects analysed	14 parents.
Patient characteristics and comparability of groups	The average age of the children is 14.6 years (from 6.6 to 23 years). 7 had a congenital heart disease. 4 have prosthetic heart valves and 3 have primitive pulmonary hypertension.
Results for primary endpoint	/
Results for second endpoint(s)	Theory assessment: All the patients passed the theory assessment. Practical assessment of carrying out the H-INR: In the 4 weeks following the start of the programme 5 parents asked for additional information on how to take a blood sample properly from the child's finger (demonstration not appropriate for small children). No parent had any further difficulties with regard to taking a blood sample from their child's finger after additional training. The average number of contacts with the coordinator is 11.4 during the 26 weeks of follow-up (between 5 and 25 contacts). The contacts were mainly to do with reporting INR results, monitoring frequency and the warfarin treatment. The mean H-INR is 2.63 (SD 0.98, 95% CI 2.42 to 2.83). The mean C-INR is 2.68 (SD 1.13, 95% CI 2.44 to 2.92). $\rightarrow$ No statistical difference between the two means. H-INR > C-INR in 35.6% of the tests. H-INR < C-INR in 41.4% of the tests. H-INR = C-INR in 23% of the tests. Correlation r^2 = 0.949, IC 95%: 0.926 to 0.965, p<0.0001. The mean interval between INR tests is 15.64 days (from 7 to 28 days). The mean number of combined H-INR and C-INR tests is 7.4 (4 to 14). The therapeutic range is achieved in 65.5% of H-INR tests and 64.4% of C-INR tests. The Bland and Altman analyses identify a difference of -0.055 units between C-INR and H-INR (only 3 results are outside acceptable limits (95%: - 0.711 to 0.601), but remain within the therapeutic range). Assessment of satisfaction: Parent satisfaction assessed on a scale of 1 to 10 is 9.4 (6.5 to 10). Only one parent expressed concern about continuing with self-monitoring (problems with their adolescent child). All the other parents wanted to continue with self-monitoring if such a programme was

	set up.
Side-effects	No major bleeding or thrombotic event during the study period.

Reference code / Study name	**Newall F, Bauman M. Point-of-care antithrombotic monitoring in children. Thromb Res. 2006; 118: 113-21.**
Study design	Literature review.
Study dates and duration	Research by Medline between 1966 and 2004.
Study objective	List of the various studies carried out on point of care monitoring of OAT in children
Devices used	CoaguChek (Roche Diagnostics). Protime Micro-coagulation system (International Technidyne Corp.). RapidpointCoag (Bayer Diagnostics). Hemochron Jr.Signature (International Technidyne). In most of the studies CoaguChek is analysed.
METHODS	
Inclusion criteria	Child treated with OAT. OAT is warranted by thromboprophylaxis as part of congenital heart diseases, including those with prosthetic heart valves, deep-vein thromboses, nephrotic syndromes and for other non-specified reasons. All the studies relate solely to patients being treated with warfarin, apart from one which also includes patients being treated with phenprocoumon. The keywords used for the Medline search are: “oral anticoagulation, point of care monitoring, antithrombotic monitoring, anticoagulant monitoring, and international normalized ratio (INR).”
Non-inclusion criteria	/
Study setting and site	3 publications out of 4 come from a single site (Canada).
Methods	Research by Medline between 1966 and 2004, keyword search. 6 publications analysed (including 1 abstract) are identified and published from 1995 to 2003. 4 paediatric studies are reported (prospective cohort studies) and 2 studies involve children and adults.
RESULTS	
Number of subjects analysed	The number of patients included in the 4 paediatric studies varies from 14 to 60 children. The number of analyses ranges from a simple INR test per patient to several tests in the same cohort of children with a total of 599 samples for 40 children.
Duration of follow-up	Not applicable
Patient characteristics	The age of the children in the 4 paediatric studies varies from 3 months to 18 years. The 2 studies involving children and adults are less informative in terms of specific paediatric details.
Results	The coagulometer analysed in 3 of the 4 studies is CoaguChek. The other study is an analytical study comparing 4 different coagulometers. The purpose of 3 of the studies was to evaluate clinical safety. 2 of them also compare the coagulometer with a conventional laboratory method. The protocols for verifying the accuracy of the coagulometers were different in the studies and no team had defined beforehand any acceptable concordance requirement between the measurements. With regard to training programmes, 2 publications (Marzinotto and Massicotte) mention training programmes being set up, but details of these programmes are not provided. There is no training programme model. 3 out of 4 studies report good concordance between the coagulometers and the conventional laboratory method. The correlation coefficients range between 0.83 and 0.96. The 2 studies which include home monitoring mention the patients’ preference for using coagulometers and the patients’ satisfaction.

Side-effects	The incidence of severe adverse effects was not clearly documented in the publications.
Authors' conclusion	This literature review points out that coagulometers for patient self-monitoring of oral anticoagulation treatment offers numerous benefits for children. The following problems in particular are encountered with children: - Numerous INR fluctuations and especially in children (environmental factors: infections, diet etc.). - Need to carry out numerous INR tests each month in order to achieve the therapeutic range. - Venous access is difficult in children. - Disruption to quality of life (needle phobia, numerous trips to hospitals/clinics, absence from school etc.). However, the studies actually carried out have a large number of limitations. Limitations of these studies: - Low-power studies: small population. No controlled or cross-over, prospective randomised study. No comparative studies on the patients followed up using coagulometers versus patients followed up using standard methods. - The methods for obtaining INR results at home versus in the laboratory vary according to the publications. - No standardised, validated data on the education and training programmes. No guidelines for use with children. - No clear definition of "thromboembolic events" and "major bleeding" in the studies, which makes it impossible to determine the incidence of bleeding and thromboses associated with coagulometers. The authors mention that additional studies need to be carried out.