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HALO Clinical Study
A single arm, prospective, non-randomized, multi-center clinical investigation of the SJM™ Masters HP™ 15mm Rotatable Mechanical Heart Valve
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Sponsored by:
Abbott
5050 Nathan Lane North
Plymouth, MN 55442

Abbott

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1 INTRODUCTION

1.1 Background Information

The current commercially available mechanical mitral valves range in sizes from 16mm to 37mm. The mitral annulus in young pediatric patients can range from 12mm to 30mm with a mean of 18mm.[1] A mitral valve annulus will typically require a sewing diameter of approximately 2mm larger than the valve size. As a 16mm valve is currently the smallest diameter valve on the market there is a portion of the pediatric population that would benefit from the availability of a smaller diameter valve.

Evidence exists to suggest that oversized valves are associated with increased mortality and morbidity rates particularly in the very young patient population.[1-4] A small mitral annulus can rarely be enlarged to accept a prosthesis larger than its diameter.[5] Intraoperative problems associated with implantation of a mitral prosthesis too large for the size of the annulus include damage to the conductive system, obstruction of the left ventricular outflow tract (LVOT), impairment of valve mobility, and damage to the left circumflex artery.[2,6] The need for pacemaker insertion after mitral valve replacement due to interruption of the conduction system of the heart has been estimated at 5-16%.[1,3-7] Mismatch of the annulus size and the prosthesis can also lead to mitral stenosis necessitating a second valve replacement procedure.[5,8,9]

1.2 Disease to be Treated

Mitral valve disease can be the result of congenital valve anomalies such as mitral stenosis, mitral insufficiency and complete or partial atrioventricular canal. Other causes of mitral valve disease include endocarditis, rheumatic heart disease, and mitral insufficiency associated with Marfan syndrome .[5,10] Approximately half of pediatric patients requiring mitral valve replacement have previously had valvuloplasty or valvulotomy to repair the diseased valve.[4-7,10,11]

1.3 Current Treatment Options

Surgical reconstruction to repair the mitral valve is the optimal treatment in the pediatric population. Surgical repair can in some cases eliminate the need for future mitral valve replacement and in other cases postpone it.[2,4,7,11] The pulmonary autograft technique described by Ross and Yacoub and modified by Kabbani has shown promise in those patients with mitral valves that have an effective orifice area of at least 3cm^2.[5,7]

When the mitral valve cannot be repaired surgically the only remaining treatment option is replacement with a prosthetic valve.[7] A second and sometimes third valve replacement after initial mitral valve replacement is expected in the very young pediatric population. The rate of mitral valve re-operation reported in the literature for patients younger than five years of age is approximately 40%.[4,7,10,11]

Mechanical valves are generally chosen over bioprosthesic valves when a very small size is required because they exhibit better hemodynamic characteristics than bioprostheses.[5] Valve replacement with allografts and xenografts are reported to show poor durability in pediatric patients.[5] In addition, the rate of premature calcification observed with bioprostheses appears to be high in this population.[2,7,8,11]

2 INVESTIGATIONAL DEVICE

2.1 Device Name

SJM™ Masters HP™ 15mm Rotatable Mechanical Heart Valve (15mm MHV).

2.2 Device Description

The investigational device is a 15mm, rotatable, bileaflet mechanical heart valve designed for implantation in the mitral position. This valve is part of the SJM™ Masters HP™ Series product line. The Hemodynamic Plus (HP) model has been designed to maximize effective orifice area. This is made possible by removing the sewing cuff from the annulus.

2.3 Intended Use

The 15mm MHV is intended for use as a replacement mitral valve in patients five years or less of age with a diseased, damaged, or malfunctioning mitral valve. This device may also be used to replace a previously implanted prosthetic mitral heart valve.

3 STUDY DESIGN

The study is a single arm, prospective, non-randomized, multi-center clinical investigation.

3.1 Study Duration

Each enrolled subject will be assessed at baseline, procedure, post-procedure, 30 days, six months, 12 months, and annually thereafter for as long as the valve remains implanted. Each enrolled subject will be followed for five years from the date of implant, until subject withdrawal, or until study closure, whichever occurs earliest.

4 STUDY PURPOSE AND OBJECTIVE

4.1 Purpose

The purpose of the study is to provide evidence of safety and effectiveness to support a supplement to the St. Jude Medical Masters Series PMA (P810002) for approval of the 15mm MHV.

The rationale for this study is to offer a replacement mitral valve for patients with anatomy that is too small for the currently commercially available valves ranging in size from 16mm to 37mm.

4.2 Objective

The objective of this study is to evaluate the safety and effectiveness of the 15mm MHV in subjects five years or less of age with a diseased, damaged, or malfunctioning mitral heart valve. The objective will be evaluated by assessing valve-related adverse events, subject survival, subject growth, and echocardiogram assessment of hemodynamic function through the five year follow-up visit as long as the valve remains implanted.

5 ENDPOINTS

5.1 Primary Safety Endpoint

The primary safety endpoint for this study is the actuarial (Kaplan-Meier) rate of total valve-related adverse events experienced through 365 days post implant or until the valve is removed/replaced due to anatomical growth of the subject, whichever occurs first. Valve-related adverse events to be evaluated are:

- Death
- Endocarditis
- Hemorrhage (whether or not due to anticoagulant/antiplatelet medication) [all and serious]
- Nonstructural dysfunction (including perivalvular leak [all and serious], hemolysis, and hemolytic anemia)
- Reoperation (including valve explant, not due to anatomical growth of the subject) [all and valve-related]
- Structural valve deterioration
- Thromboembolism
- Valvular thrombosis

5.2 Primary Effectiveness Endpoints

The primary effectiveness endpoints in this study include the following:

1. Survival at 12 months post implant or survival until the valve is removed/replaced due to anatomical growth of the subject, whichever occurs first.
2. Peak gradient as assessed by echocardiography at 12 months post implant or when the valve is removed/replaced due to anatomical growth of the subject, whichever occurs first.
3. Mean gradient as assessed by echocardiography at 12 months post implant or when the valve is removed/replaced due to anatomical growth of the subject, whichever occurs first.

4. Valvular regurgitation as assessed by echocardiography at 12 months post implant or when the valve is removed/replaced due to anatomical growth of the subject, whichever occurs first.

5.3 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints include the following:

1. Increase in percentile ranking on the CDC growth chart for height at 12 months post implant or until the valve is removed/replaced due to anatomical growth of the subject, whichever occurs first, compared to baseline.
2. Increase in percentile ranking on the CDC growth chart for weight at 12 months post implant or until the valve is removed/replaced due to anatomical growth of the subject, whichever occurs first, compared to baseline.

CDC growth charts are provided in Appendix 3.

6 STATISTICAL ANALYSIS

6.1 Statistical Analysis and Reporting

Kaplan-Meier adverse event rates with 95% confidence intervals and early rates will be calculated for all safety and survival endpoints.

Hemodynamic function will also be evaluated at each visit for each of the following variables:

- Mean pressure gradients across the mitral valve
- Peak pressure gradients across the mitral valve
- Cardiac output
- Cardiac index
- Valvular regurgitation (and the site, as appropriate)

7 RISK/BENEFIT ANALYSIS

7.1 Potential Benefits

Replacement of a diseased mitral valve with the 15mm MHV may improve hemodynamic function of the valve thereby providing the opportunity for improved physical growth and development. An additional potential benefit of receiving an appropriately sized mitral valve replacement is avoidance of complications associated with implantation of a mitral prosthesis too large for the size of the annulus which may include damage to the conductive system, obstruction of the left ventricular outflow tract (LVOT), impairment of valve mobility, and damage to the left circumflex artery.

7.2 Potential Risks

Potential risks of receiving a mechanical mitral valve include:

- The need for a second valve replacement due to either dehiscence, valve failure or malfunction, development of mitral stenosis, unacceptable hemodynamic status or eventual somatic outgrowth.
- Heart failure requiring cardiac transplant.
- Cardiac arrhythmia with or without the need of pacemaker implantation.
- Hemolysis potentially resulting in anemia with or without splenomegaly and/or development of cholelithiasis.
- Infection including but not limited to endocarditis, myocarditis, cellulitis and/or septicemia.
- Thromboembolism or hemorrhage causing stroke, myocardial infarction or other significant impairment.
- Obstruction or distortion of adjacent cardiac structures.

All of the identified risks have the potential to result in death. The mortality rate reported for mitral valve replacement in the pediatric population is highly variable and ranges between approximately 5 and 30%.[3,7,12-15]

7.3 Risk Minimization

Risks will be minimized by selecting Investigators that:

- Have experience implanting mechanical mitral valves in patients under the age of five.
- Appreciate the need for closely monitoring and managing anti-coagulation regimens.
- Are willing to partner with the subject's personal cardiologist to ensure appropriate care and follow-up.

8 ELIGIBILITY CRITERIA

8.1 Eligibility Criteria for Pivotal IDE Subjects

A subject is eligible to participate in the study if he/she meets all inclusion criteria and meets no exclusion criterion.

8.1.1 Inclusion Criteria for Pivotal IDE Subjects

1. Subject requires mitral valve replacement.*
2. Subject's legally authorized representative gives written consent to participate in the clinical study.
3. Subject is willing and able to return for data collection and follow-up for the duration of the clinical study.

*Subjects undergoing concomitant procedures (e.g. valve repair) are eligible for this study other than those noted in the exclusion criteria.

8.1.2 Exclusion Criteria for Pivotal IDE Subjects

1. Subject is > 5 years of age.
2. Subject has a contraindication to anticoagulant/antiplatelet medication.
3. Subject has a prosthetic valve(s) at a site other than the mitral valve prior to the study procedure.*
4. Subject requires concomitant replacement of the tricuspid, pulmonary, or aortic valve.
5. Subject has active endocarditis.
6. Subject has active myocarditis.
7. Subject has had an acute preoperative neurological deficit that has not returned to baseline or stabilized ≥ 30 days prior to the study procedure.
8. Subject has had an acute cardiac adverse event that has not returned to baseline or stabilized ≥48 hours prior to the study procedure.
9. Subject has a non-cardiac illness resulting in a life expectancy of < 1 year.
10. Subject has a known requirement for additional cardiac surgery within 12 months after the study procedure.
11. Subject has been previously enrolled and implanted in this study.
12. Subject is participating in another study for an investigational drug and/or device.
13. Subject has any other medical condition that in the opinion of the Investigator will interfere with the study results.

*Subjects who have undergone a previous Ross procedure of the pulmonary valve are eligible for this study.

8.2 Eligibility Criteria for Adjunctive Subjects

In an effort to ensure data on all real-world use conditions are consistently collected and reported on, a subject is eligible to participate in protocol Revision C if he/she meets all of the following inclusion criteria and meets no exclusion criterion. Separate criteria are presented below for the two arms of adjunctive subjects of Revision C (Adjunctive Prospective Subjects in Sections 8.2.1 and 8.2.2 and Adjunctive EU/CU Subjects in Section 8.2.3).

8.2.1 Inclusion Criteria for Adjunctive Prospective Subjects

1. Subject requires mitral valve replacement.*
2. Subject's legally authorized representative gives written consent to participate in the clinical study.
3. Subject is willing and able to return for data collection and follow-up for the duration of the clinical study.

*Subjects undergoing concomitant procedures (e.g. valve repair) are eligible for this study.

8.2.2 Exclusion Criteria for Adjunctive Prospective Subjects

1. Subject is > 5 years of age.
2. Subject has a contraindication to anticoagulant/antiplatelet medication.

8.2.3 Eligibility Criteria for Adjunctive EU/CU Subjects

In order for Adjunctive EU/CU Subjects with a previous implant attempt to be eligible for study participation, the following criteria must be met:

1. The subject must have been ≤ 5 years of age at the time of mitral valve replacement with the 15mm MHV.
2. An implant was attempted with the 15mm MHV, where implant attempt is defined as the device physically contacting the subject's cardiac anatomy.
3. The legally authorized representative signs the study informed consent for this protocol allowing access to all relevant historical medical information and prospective follow-up (if applicable).
4. Either
   (a) the legally authorized representative and site agree to follow the subject per the assessment schedule and complete all required assessments per this protocol from the time of consent going forward. OR
   (b) the subject's status is deceased or explanted, but an implant with 15mm MHV was attempted.

9 STUDY PARTICIPATION

9.1 Screening and Informed Consent

This study will be performed in accordance with applicable confidentiality, privacy and security, and data protection laws. The subject's legally authorized representative must provide written informed consent prior to performing any protocol-required baseline testing that is not standard of care for valve procedures.

9.2 Assessment Schedule

All enrolled subjects will be assessed according to the following schedule for as long as the valve is implanted.

Table 1: Assessment Schedule

ASSESSMENTS	Baseline	Procedure	Post-Procedure[1] (+ 24 hours)	30 Days[1] (± 14 days)	6 Months[1] (± 30 days)	12 Months[1] (± 60 days)	Annual Visits through 60 Months[1] (± 60 days)	Explant (Prior to procedure)
Medical History	X							
Physical Exam (PE)	X		X	X	X	X	X	X
Transthoracic Echocardiogram (TTE)[2]	X		X	X	X	X	X	X
Blood Collection[3]	X		X	X	X	X	X	X
Anticoagulant/Antiplatelet Medication Collection	X	X	X	X	X	X	X	X
Adverse Event Collection[4]		X	X	X	X	X	X	X
Adverse Event Follow-up[5]			X	X	X	X	X	X

1. Visits are to occur as long as the valve remains implanted.
2. The study specifies TTE rather than transesophageal echocardiography (TEE) to minimize subject risk. Echocardiographic data collected from TEE warranted for any other medical purpose is allowed.
3. Plasma free hemoglobin for hemolysis evaluation. Spot urine urobilinogen is an acceptable alternative if a non-hemolyzed blood sample cannot be obtained.
4. Refer to section 15.2 for a list of adverse events that are required to be collected and reported.
5. Required only for subjects who have an unresolved adverse event.

9.3 Baseline

Obtain written informed consent from the subject's legally authorized representative prior to conducting any study-related testing that is not considered standard of care for valve procedures. All baseline tests must occur prior to the procedure. It is preferable if the testing is completed no more than one month prior to the procedure date.

The following baseline assessments are required:

- Medical history
- Physical exam
- Transthoracic echocardiogram
- Blood collection (Plasma free hemoglobin for Hemolysis evaluation). Spot urine urobilinogen is an acceptable alternative if a non-hemolyzed blood sample cannot be obtained.
- Anticoagulant/antiplatelet medication collection

For Adjunctive EU/CU Subjects, baseline assessments should be collected from subject's medical records, when available, for visits conducted prior to enrollment.

9.4 Procedure

The 15mm MHV is implanted surgically pursuant to the Instructions for Use.

The following assessments are required at the time of the procedure:

- Anticoagulant/antiplatelet medication collection
- Adverse event collection

For Adjunctive EU/CU Subjects, procedure assessments should be collected from subject's medical records, when available, for procedures conducted prior to enrollment.

9.5 Post-Procedure

If the subject does not have the 15mm MHV implanted the subject should be discontinued from the study and followed per the physician's standard of care.

As there are insufficient data to indicate otherwise, the sponsor recommends that subjects implanted with the 15mm MHV be routinely maintained on anticoagulants unless, for other reasons, it is not medically indicated.

The following assessments are required after the enrolled subject leaves the surgical suite with the valve implanted. These assessments must be completed at least 24 hours after the procedure:

- Physical exam

- Transthoracic echocardiogram
- Blood collection (Plasma free hemoglobin for Hemolysis evaluation). Spot urine urobilinogen is an acceptable alternative if a non-hemolyzed blood sample cannot be obtained.
- Anticoagulant/antiplatelet medication collection
- Adverse event collection
- Adverse event follow up

For Adjunctive EU/CU Subjects, post-procedure assessments should be collected from subject's medical records, when available, for visits conducted prior to enrollment.

9.6 Post-Procedure Anticoagulation Recommendation

As there are insufficient data to indicate otherwise, the sponsor recommends that patients implanted with the 15mm MHV be routinely maintained on anticoagulants to avoid the risk of thrombus formation and thromboembolic complications, unless it is not medically indicated.

The recommended anticoagulation therapy for patients implanted with the 15mm MHV are based on the 2013 AHA Guidelines for the Prevention and Treatment of Thrombosis in Pediatric Patients[24] in combination with experience from subjects previously enrolled in this study.

Acceptable forms of anticoagulants include intravenous unfractionated heparin or oral warfarin. When using warfarin the recommended target INR is 2.5 to 3.5 for valves implanted in the mitral position in the absence of risk factors for thrombus formation. In the presence of risk factors consider using a higher target INR or adding aspirin to therapeutic warfarin. Risk factors include first 3 months post-implant, younger age (< 6 months), small size (<6 kg), low flow state, unreliable oral intake, previous thromboembolism, and hypercoagulable condition. Home INR monitoring may be associated with a reduced rate of complications. Use of low molecular weight heparin may be associated with an increased rate of complications based on input from HALO IDE investigators.

In patients receiving warfarin, the INR should be monitored daily until therapeutic levels are achieved, and then may be decreased in frequency when stable with a minimum of monthly testing. The INR should be tested whenever there is illness or with any changes in medication or diet.

The final choice for anticoagulation therapy is left to the clinical judgement of the investigator.

9.7 Additional Follow-up

Protocol required follow-up visits should be completed by the Investigator. To aid in subject follow-up compliance, subjects can return to their primary cardiologist for follow up visits but data must be obtained by the Investigator for review and submission to the Sponsor.

Investigators should inform cardiologists of all required follow-up tests prior to the visit and every effort should be made to obtain complete tests results with all required data points after the visit occurs. Protocol deviations will be required for all missed testing (refer to section 17.2.5 Protocol Compliance).

The following assessments are required at follow-up visits at the intervals noted on the assessment schedule in section 9.3 for all enrolled subjects that have the valve implanted:

- Physical exam
- Transthoracic echocardiogram
- Blood collection (Plasma free hemoglobin for Hemolysis evaluation). Spot urine urobilinogen is an acceptable alternative if a non-hemolyzed blood sample cannot be obtained.
- Anticoagulant/antiplatelet medication collection
- Adverse event collection
- Adverse event follow-up

For Adjunctive EU/CU Subjects, additional assessments should be collected from subject's medical records, when available, for visits conducted prior to enrollment.

10 Discontinuation

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize the subject's future medical care or relationship with an Investigator. All reasonable efforts should be made to retain the subject in the clinical study until study completion. Subjects will be asked what the reason for termination/withdrawal is but have the right not to answer.

The Principal Investigator may also withdraw a subject from the study at any time if he/she believes it is in the subject's best interest.

11 ECHOCARDIOGRAPHY PROCEDURES

Hemodynamic function will be evaluated by calculating the number of observations, mean, standard deviation, minimum and maximum values for each of the following variables:

- Mean pressure gradients across the mitral valve
- Peak pressure gradients across the mitral valve
- Cardiac output
- Cardiac index
- Valvular regurgitation

Transthoracic echocardiogram (TTE) examinations are required for each subject at baseline, post-procedure, 30 days, 6 months, 12 months, and annually thereafter for as long as the valve remains implanted.

The study specifies TTE rather than transesophageal echocardiography (TEE) to minimize subject risk. Echocardiographic data collected from TEE warranted for any other medical purpose is allowed.

For Adjunctive EU/CU Subjects, echocardiograms should be collected from subject's medical records, when available, for visits conducted prior to enrollment. Additionally, echocardiograms should be collected even if any echocardiographic assessments occurred outside of a specified visit window as they may be used as supporting source documentation on the subject.

CDs of the echocardiography exams from each required visit will be forwarded to the echocardiography core laboratory (core lab) for interpretation. The primary responsibility of the core lab is to provide consistent interpretation of TTE data across all study sites by completing the TTE Case Report Form (CRF).

The sponsor will use only the measurements from the core lab for analysis. If the core lab determines the echocardiogram is unreadable, the subject may be asked to return for another echocardiogram.

12 BLOOD COLLECTION

Plasma free hemoglobin will be collected and analyzed for hemolysis at baseline, post-procedure, 30 days, six months, 12 months, and annually thereafter for five years as long as the valve remains implanted. Spot urine urobilinogen is an acceptable alternative if a non-hemolyzed blood sample cannot be obtained.

13 DATA COLLECTION PROCEDURES

13.1 Data Entry and CRF Submission

All required data will be recorded on standardized specific Case Report Forms (CRFs).

14 INVESTIGATIONAL DEVICE HANDLING

The sponsor will control the availability of the study valve by shipping valves only to qualified study Investigators who have IRB and sponsor approval. The sponsor will keep records that indicate the destination and date of shipment. Study valves are not transferable between Investigators unless prior written approval is obtained from the sponsor.

14.1 Accountability

Upon receipt of the 15mm MHV, Investigators will maintain the following accurate, complete, and current records relating to device accountability (21 CFR 812.140 (2)):

Records of receipt, use or disposition of study valves including:

- Type and quantity
- Date of receipt
- Location
- Expiration date
- Serial number
- Names of all persons who received, used or disposed of each unit, and
- Why and how many units of the study valve have been used, returned to the Sponsor, repaired, or otherwise disposed of.

All study valves must be accounted for on the Device Disposition Report even if they are not used.

14.2 Storage

The sponsor requires that all study valves be stored according to the labeling, in a secure area to prevent unauthorized access or use. The study site will prevent use of the investigational product for non-investigational procedures.

14.3 Returns

Valves which are expiring, not successfully implanted or are explanted should be returned to the sponsor. All unused 15mm MHV product must be returned to the sponsor at the completion of the study.

Prior to returning study valves, contact the sponsor clinical study team to obtain a return number. Communicate the serial numbers for all valves being returned. After the return number is received, update the applicable Device Disposition Report(s) with the new disposition of the valve, reason for return, and return number. Send a copy of the updated report to the clinical study team by email. Keep the original for your records.

Ensure all opened product is clearly identified. If possible, return the valve in its original packaging and include all components (e.g. valve holder). Include a copy of the Device Disposition Report(s) with the items being returned. Write the return number on the outside of the package and ship to the address provided with the return number.

15 SAFETY

Safety will be evaluated through the analysis of adverse events related to the 15mm MHV. All valve-related adverse events will be collected and adjudicated by the Data Safety Monitoring Board (DSMB) in accordance with Akins *et al.*[25]

15.1 Adverse Event Definitions

Adverse Event:

An adverse event (AE) is any undesirable clinical occurrence that is a negative change from baseline.

Unanticipated Adverse Device Effect (UADE):

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the Investigational Plan including a supplementary plan or application); or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Serious Adverse Event:

Serious adverse events will be defined as those adverse events resulting in the following; death, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospital stay, persistent or significant disability/incapacity or medically significant event.

Non-serious Adverse Event:

Non-serious adverse events will be defined as those events requiring health care professional directed medical intervention but that are not life threatening, and are not likely to have long-term (> 6 months) sequelae, and do not require long term (> 6 months) therapy.

Anticipated Adverse Events:

Complications associated with replacement mechanical heart valves include, but are not limited to:

- hemolysis;
- infections;
- thrombus;
- thromboembolism;
- valve dehiscence;
- unacceptable hemodynamic performance;

- hemorrhagic complications secondary to anticoagulant medication;
- prosthetic failure;
- heart failure;
- damage to other cardiac structures including the cardiac conduction system;
- obstruction or distorting of adjacent cardiac structures; or
- death.

Any of these complications may require reoperation or explantation of the study valve.

15.2 Adverse Event Reporting

15.2.1 Timeline for reporting Serious Adverse Events

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than **3 calendar days** from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB according to the institution's IRB reporting requirements.

15.2.2 Reporting Valve-Related Adverse Events

Safety surveillance within this trial (and the safety reporting performed by the investigator) starts:

- as soon as the subject is enrolled for Pivotal IDE subjects enrolled under protocol revision A or B.
- as soon as the subject is enrolled for Adjunctive Prospective Subjects.
- from the time of attempted initial implant (defined as the device physically contacting the subject's cardiac anatomy) for enrolled Adjunctive EU/CU Subjects.

Safety surveillance and safety reporting will continue until the last study visit has been performed, or the subject is deceased, or the subject concludes participation in the trial.

Investigators are responsible for promptly reporting, as soon as they become aware, all serious and non-serious valve-related adverse events as specified in Akins et al.[25] to the sponsor by

completing the Adverse Event CRF. Serious adverse events should be reported as specified in Section 15.2.1. Reportable events include:

- Death
- Endocarditis
- Hemorrhage (whether or not due to anticoagulant/antiplatelet medication)
- Nonstructural dysfunction (including perivalvular leak, hemolysis, and hemolytic anemia)
- Reoperation (including valve explant, not due to anatomical growth of the subject)
- Structural valve deterioration
- Thromboembolism (valve-related)
- Valvular thrombosis
- Unanticipated Adverse Device Effects (UADEs)

Refer to Appendix 11 for definitions of all reportable valve-related adverse events. All unresolved adverse events should be followed by the Investigator until resolution. Updates to adverse events should be provided to the sponsor by completing the AE Follow-Up CRF.

The sponsor may request that additional information such as operative notes, clinic notes, discharge summaries, histopathology reports, or a physician's summary of the event be provided to the sponsor as supporting documentation for all reported events.

15.2.3 Reporting Unanticipated Adverse Device Effects

An Investigator shall submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than ten (10) working days after the Investigator first learns of the effect (21 CFR 812.150 (a) (1)).

15.2.4 Reporting Deaths

An Investigator shall submit to the sponsor a report of any death occurring during the study as soon as possible without undue delay. All deaths will be reported by the sponsor to the FDA within ten (10) working days of becoming aware of the death.

Send all source documents to the sponsor clinical study team via email.

15.3 Data Safety Monitoring Board (DSMB)

An independent DSMB will be formed to regularly review study progress with regard to safety. At a minimum, the DSMB will meet semi-annually. Members of the DSMB will have no affiliation with the HALO Clinical Study.

A DSMB Manual of Operations will be developed and agreed upon by the sponsor and DSMB members prior to initiation of the trial. The manual will describe the specific functions of the DSMB. The primary responsibilities of the DSMB are to:

- Establish adverse event definitions (and refine definitions as necessary during the conduct of the clinical study)
- The DSMB will act as a Clinical Events Committee (CEC) to adjudicate whether or not adverse events are valve-related and determine the severity of the events
- Review and validate the subject sample (i.e., review inclusion/exclusion deviations and other protocol deviations)
- Provide oversight for issues affecting general subject welfare
- Establish study termination guideline criteria
- Recommend premature study termination

At any time during the course of the study, the DSMB may offer opinions or make formal recommendations concerning aspects of the study that impact subject safety (e.g., safety-related protocol changes or input regarding adverse event rates associated with the investigational study). Additionally, the DSMB may act as an advisory panel for questions regarding informed consent, subject enrollment, protocol implementation, study endpoints, data discrepancies, and other issues that may present during the course of the study.

The DSMB will review all adverse events reported by the site and determine the following: adverse event type, relatedness to the procedure or device (if known), and whether the event is anticipated or unanticipated. Following each DSMB meeting a report will be sent to Investigators indicating the final adjudication of all adverse events reviewed during the meeting.

In all reports to the FDA adverse events will be pulled from the DSMB adjudication unless the adverse event has not been adjudicated, as noted in the report.

16 CONFIDENTIALITY

All subject information collected during the course of this study will be kept confidential according to applicable state and federal laws and regulations.

The FDA or other US government agencies (including regulatory agencies) and regulatory authorities in other countries may inspect and copy subject records or other information about subjects related to this study.

Any information about subjects that leaves the institution conducting the study will be modified to remove certain information that could identify the subject (e.g., subject's name, age on the day of enrollment, address, and hospital number) and only be identifiable by a subject ID code.

Study data provided to the sponsor that is published in medical journals and/or presented at scientific conferences will not allow the identification of study subjects.

Study results from this study may also be published in scientific journals or presented at conferences as an oral or poster presentation; however, the identity of a study subject will not be disclosed.

17 STUDY ADMINISTRATION

17.1 Study Sponsor

17.1.1 Clinical Project Team

A sponsor clinical project team will be developed and trained to select qualified Investigators, train investigative sites, monitor the clinical study, ensure IRB approval and renewal are obtained, and inform the IRB and FDA of any significant new information about the clinical study. The team will adhere to Abbott/ St. Jude Medical Corporation internal procedures, CFR parts 11, 54, 56, 812 and all other applicable regulations. The Sponsor will avoid improper influence on, or inducement of, the subject, monitor, any Investigators, or other parties participating in or contributing to the clinical study.

17.1.2 Amendments to the Investigational Plan

Investigational Plan amendments may occur during the course of the study and will be reviewed prior to implementation to determine if the changes affect the: validity of the data; risk-to-benefit ratio; scientific soundness of the Investigational Plan; or the rights, safety, or welfare of the human subjects involved in the clinical study.

Investigational Plan amendments that affect any of the above criteria will require FDA and IRB/EC approval prior to implementation. Amendments that do not meet the criteria above will be reported to the FDA according to 21 CFR 812.35.

17.1.3 Monitoring Procedures

Monitoring is necessary to ensure adequate protection of the rights and safety of human subjects and the quality and integrity of the data obtained during the study. It is the responsibility of the sponsor of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met. Monitoring activities will be conducted according to the Investigational Plan, Clinical Trial Agreement, ICH GCP guidelines, 21 CFR 812, and FDA guidance relevant to this clinical study.

A monitor will visit the investigator or designee periodically during the study to monitor progress, to assist in gathering the required data and to answer any questions. During

these visits, the clinical monitor will review the patient's records to verify that all records and files are up to date and assure compliance with all requirements of the protocol and FDA regulations.

The investigator will make patient and study records available to the clinical monitor for periodic inspection.

17.1.4 Publication Policy

No study results obtained under this Investigational Plan, nor any information provided to the Investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of the sponsor. Investigators are obligated to follow the sponsor publication policy, which is outlined in the Clinical Trial Agreement.

17.1.5 IRB Information

The sponsor requests waiver of the requirements under 21 CFR part 812.35(b) for submitting certification of IRB approval to the FDA prior to the beginning the study at a particular center. In lieu of this requirement the sponsor will submit an IRB/Investigator list update in six month intervals.

17.2 Study Investigators

The Principal Investigator at each site is responsible for ensuring that the HALO Clinical Study is conducted according to the Clinical Trial Agreement and all amendments thereto, the Investigational Plan, any conditions of approval imposed by applicable regulatory authorities and/or the reviewing IRBs, and all applicable laws and regulations. All Investigators shall avoid improper influence on or inducement of subjects, the Sponsor, and other Investigators participating in or contributing to the clinical study.

Investigators are responsible for obtaining informed consent prior to enrolling any subject in the clinical study. If new information becomes available during the study that can significantly affect a subject's future health and medical care, or willingness to continue in the study, that information will also be provided to the subjects in written form.

17.2.1 Records

Records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

17.2.2 Compliance

The sponsor will review and monitor Investigator compliance and determine if there is a need to secure compliance based on the severity and/or trends in non-compliance to

the signed Clinical Trial Agreement with Abbott (formerly St. Jude Medical), the Investigational Plan, the applicable regulations or any conditions of approval imposed by the reviewing IRB or FDA (21 CFR 812.46 (a)). Depending on the severity and/or trend in non-compliance, the Investigator may receive a formal warning or re-training through a site visit or conference call.

17.2.2.1 *Deviations to the Investigational Plan*

A deviation is used to describe a situation in which the Investigational Plan was not followed. Deviations may be identified at the site or by in-house sponsor personnel, and will be recorded on the Deviation CRF. The site is responsible for notifying their IRB and providing IRB notification to the sponsor, if applicable.

17.2.2.2 *Emergency Deviations from the Investigational Plan*

If a deviation from the Investigational Plan is necessary to protect the life or physical well-being of a subject in an emergency, the Investigator must notify the sponsor and the appropriate IRB within five (5) working days. For all other changes in, or deviations from the Investigational Plan, prior written approval from the sponsor and the IRB is required.

The FDA and IRB will be notified if the deviation affects the scientific soundness of the Investigational Plan.

17.2.2.3 *Informed Consent Compliance*

If the 15mm MHV is used without obtaining informed consent, the Investigator will report such use to the sponsor and the appropriate IRB within five (5) working days with an explanation of the circumstances of such use per 21 CFR 812.150(a)(5).

Informed consent deviations may include, but are not limited to:

- Failure to obtain consent from the subject's legally authorized representative
- Failure to obtain the signature of the subject's legally authorized representative
- Failure to obtain date (and time, if required) of signature of the subject's legally authorized representative
- Failure to obtain legally authorized representative initials on each page, if applicable
- Failure to obtain signature of person conducting the informed consent process
- Failure to obtain witness signature, if applicable
- Use of unapproved informed consent form
- Failure to obtain HIPAA Authorization, if applicable

17.2.3 Institutional Audits

The Investigator will permit study-related auditing and inspections of all study-related documents by the IRB, government regulatory agencies, and the sponsor. The Investigator will allocate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

17.3 Institutional Review Board (IRB)

17.3.1 Responsibilities

All IRBs must comply with applicable IRB regulations (21 CFR part 50) and IDE regulations (21 CFR part 812) in reviewing and approving device investigations. An IRB shall safeguard the rights, safety, and well-being of all study subjects.

17.3.2 Composition

The IRB shall be composed of members meeting the minimum requirements set forth in 21 CFR 56.107.

17.3.3 Initial Approval

Prior to shipment of study valves, the sponsor will require documentation of IRB approval of the Investigational Plan and the ICF. The initial IRB approval and approved ICF will be filed in the site Regulatory Binder.

17.3.4 Annual Renewal

An IRB shall conduct continuing review of the clinical study at intervals appropriate to the degree of risk posed by the device, but not less than once per year (21 CFR 56.109). A copy of the IRB renewal will be sent to the sponsor and filed in the site Regulatory Binder.

Continuation of research after expiration of IRB approval is a violation of the regulations.

The following must be completed if the IRB fails to renew the study:

- Research activities must stop if the IRB has not renewed the continuation of the study.
- Study valves must be returned to the sponsor.
- No new subjects may be enrolled into the study, and enrolled subjects cannot be seen for follow-up according to the protocol, except under the following circumstance:

    - The IRB may provide a written directive that subjects should still be seen for safety follow-up pending re-approval. Under this IRB directive, subjects should be seen for safety follow-up only, in order to assure subject safety and welfare is being overseen.
- If the Investigator is actively pursuing approval, the IRB may be flexible in permitting currently enrolled subjects to continue to be seen.
    - The sponsor will require documentation from the IRB of this decision.
    - Subjects will need to be informed that the IRB approval has lapsed, and adverse events will be reported to the IRB and the sponsor.

17.3.5 Records

Each reviewing IRB must maintain the following records (21 CFR 56.115):

- All pertinent correspondence relating to the study
- All records of membership and affiliations
- Meeting minutes

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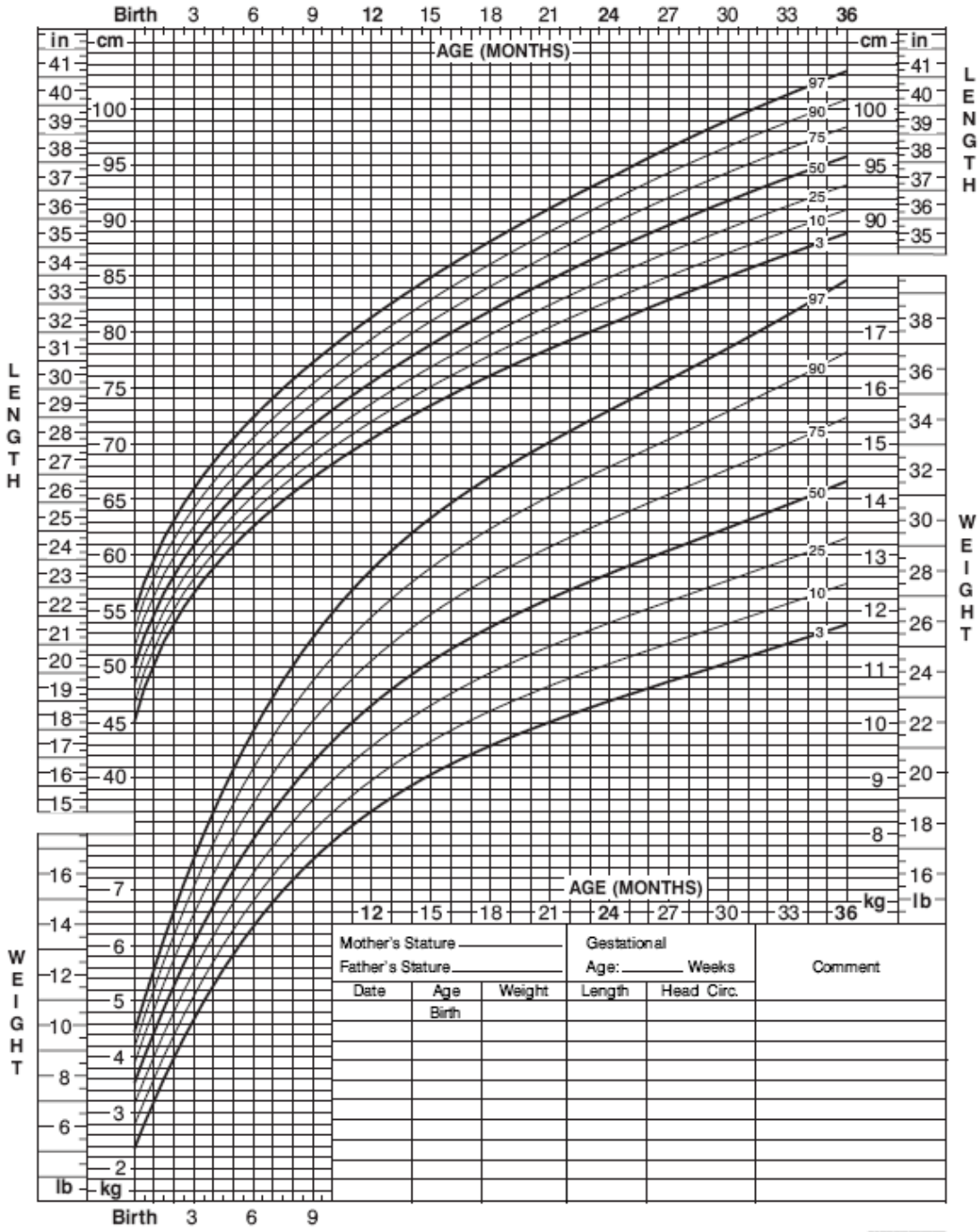
Appendix 3: CDC Growth Charts

Birth to 36 months: Boys
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



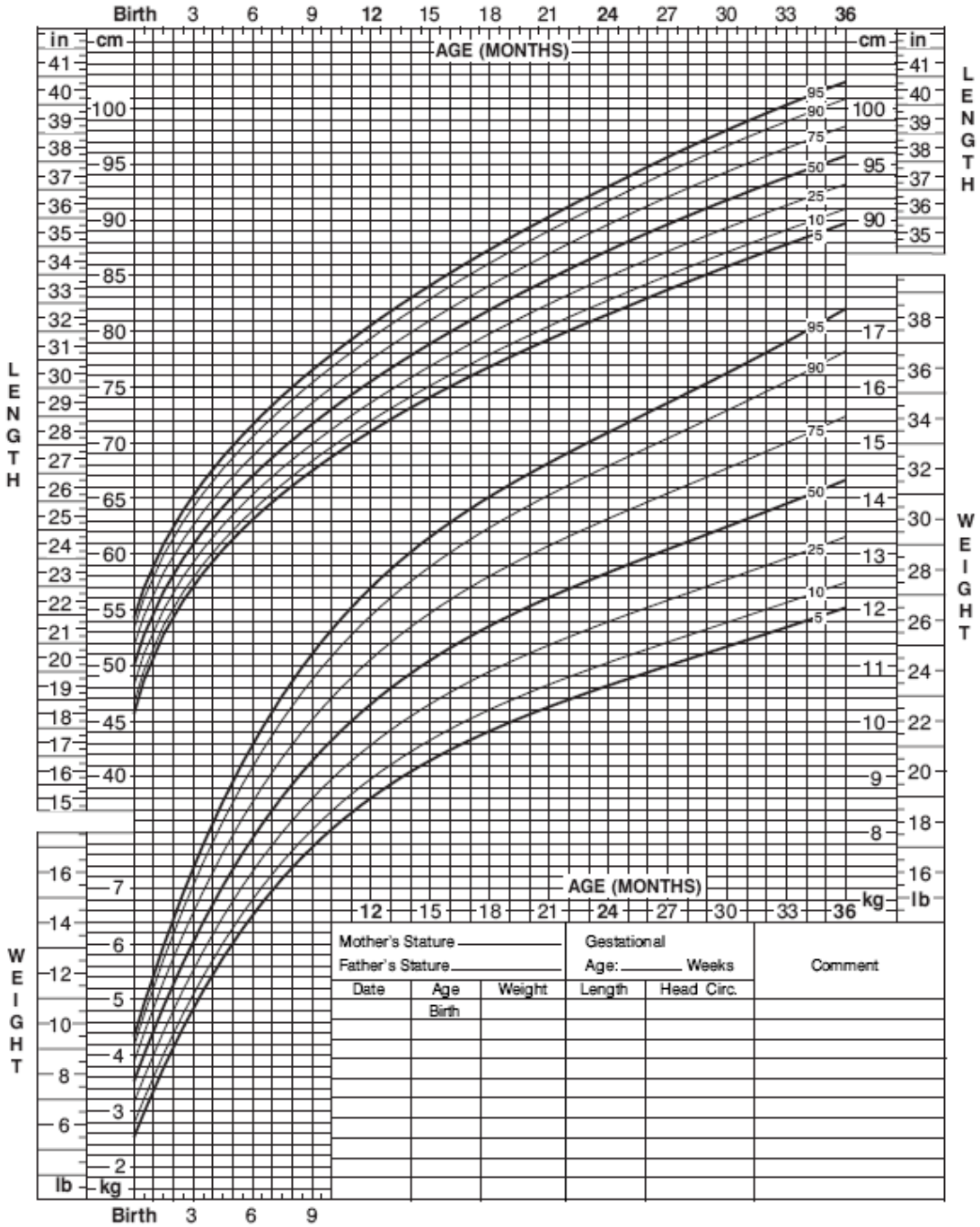
Published May 30, 2000 (modified 4/20/01).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC
SAFER · HEALTHIER · PEOPLE™

Birth to 36 months: Boys
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published May 30, 2000 (modified 4/20/01).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC
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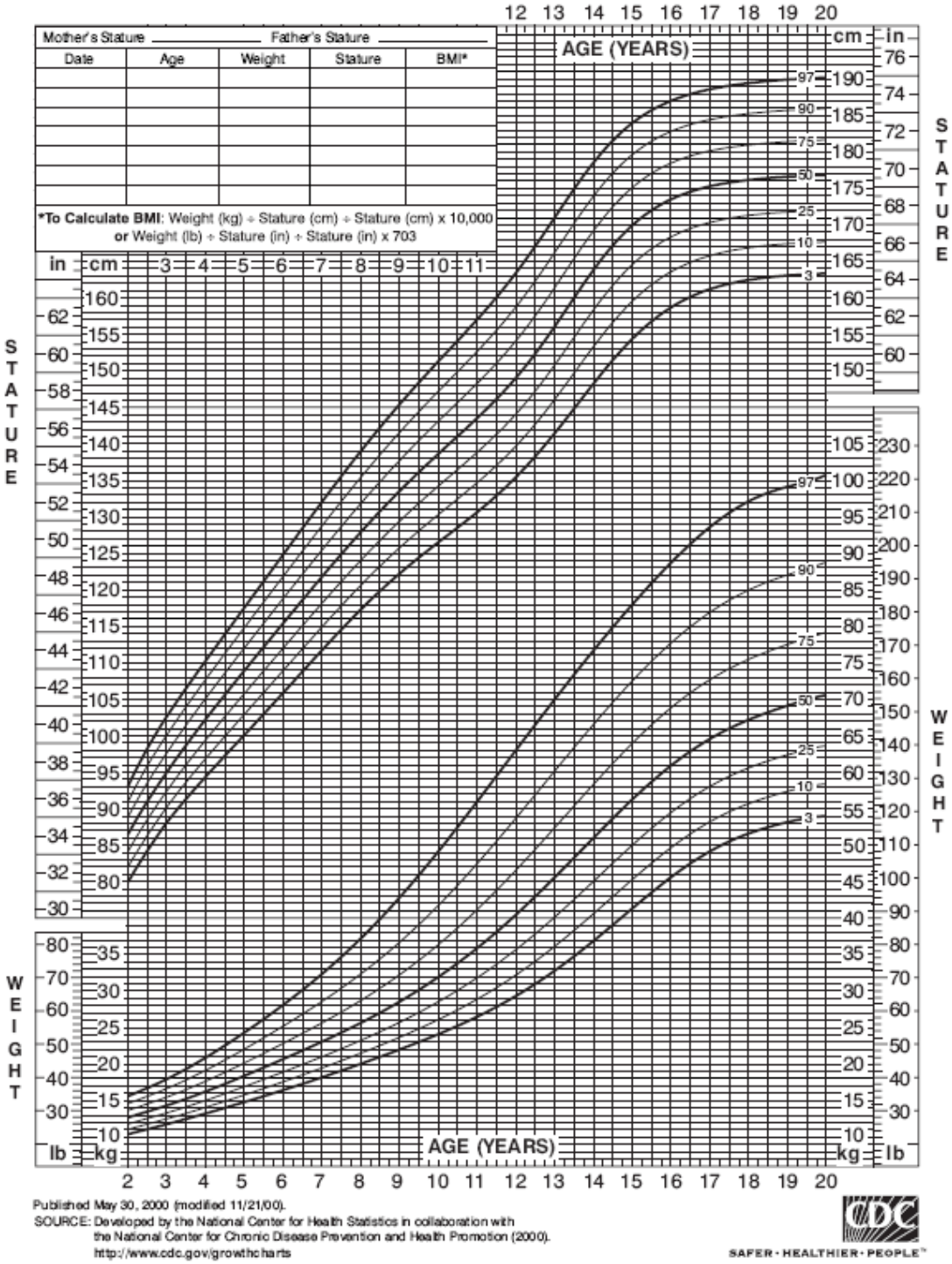
2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME _____

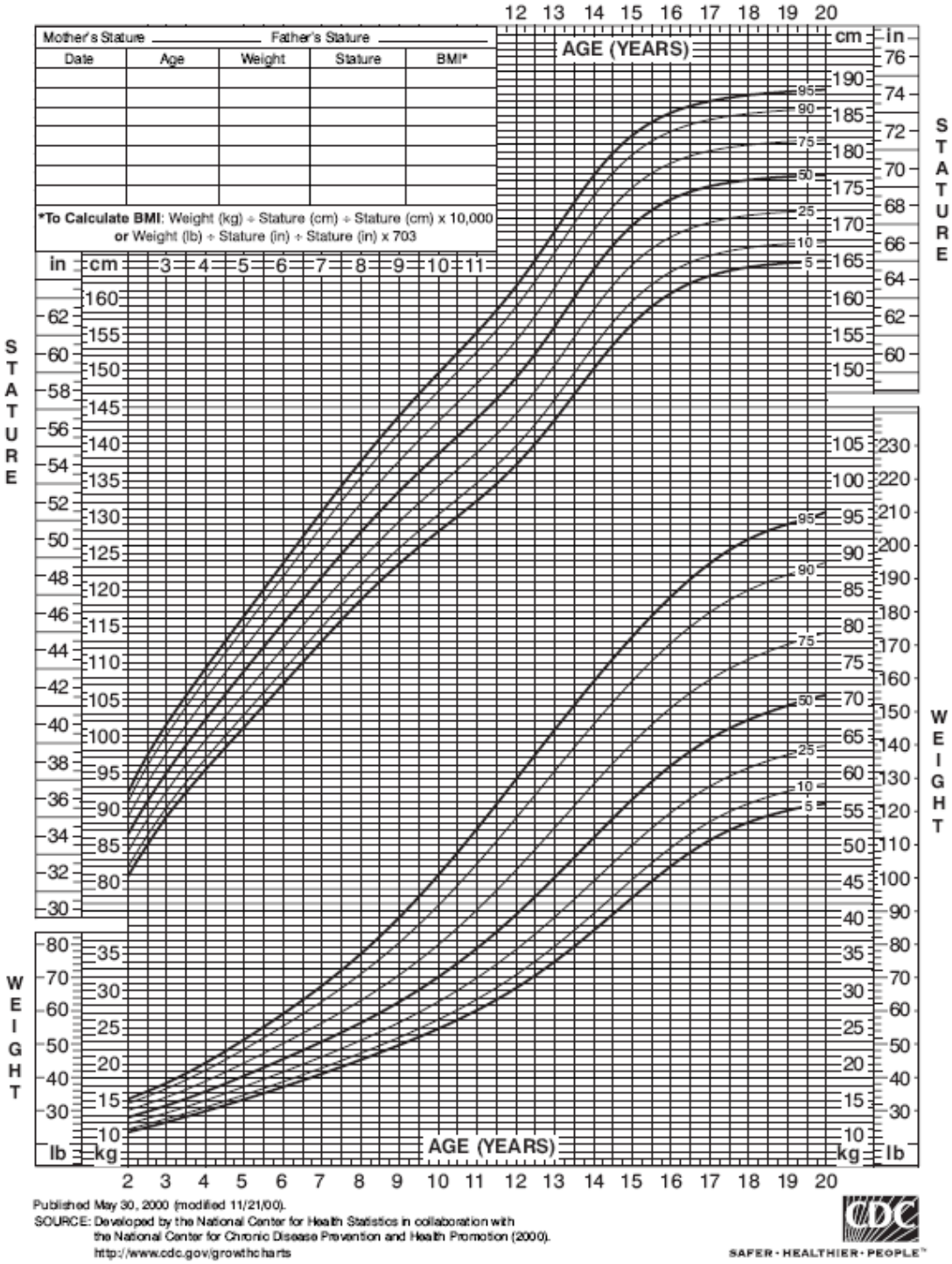
RECORD # _____



2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME _____

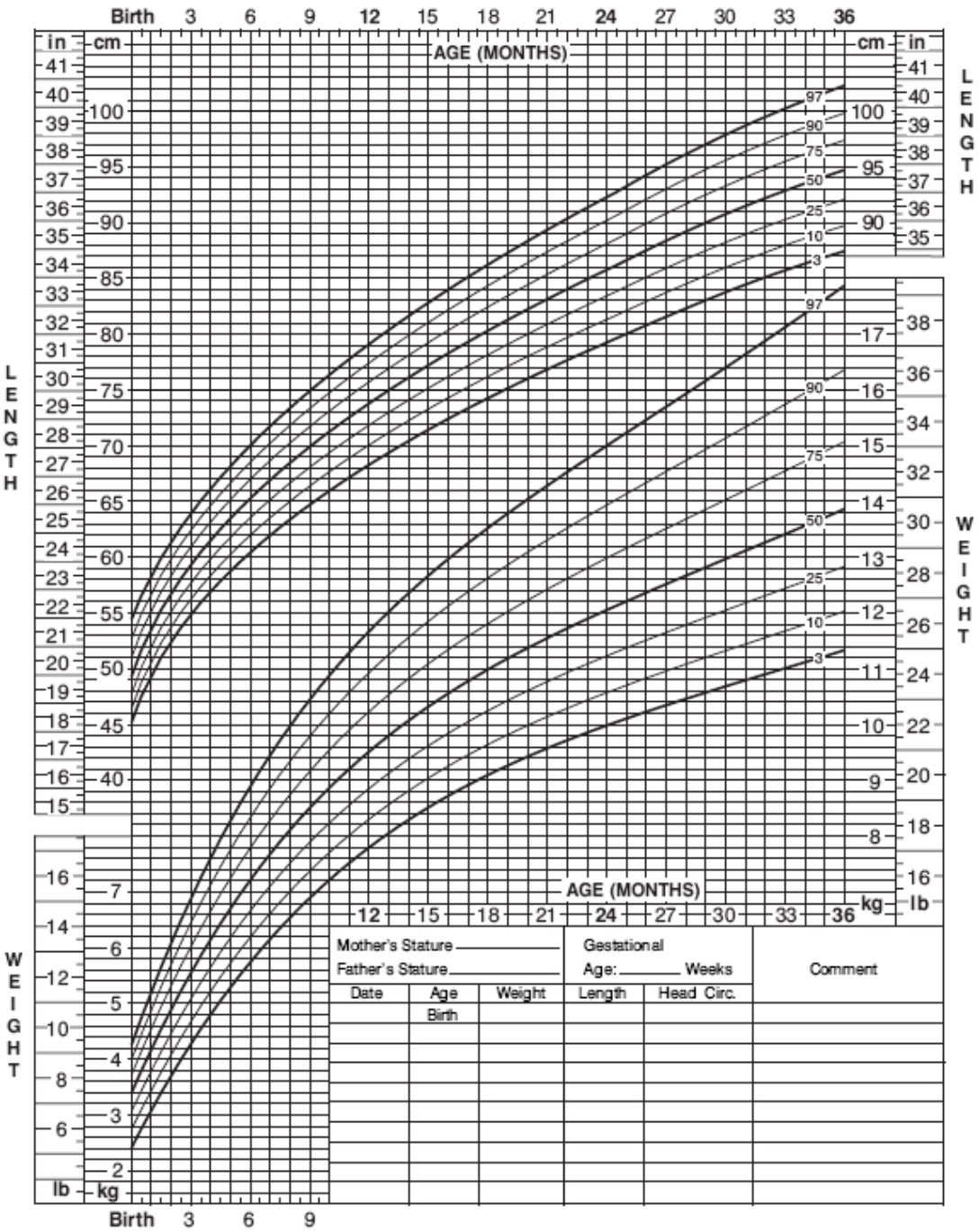
RECORD # _____



Birth to 36 months: Girls
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



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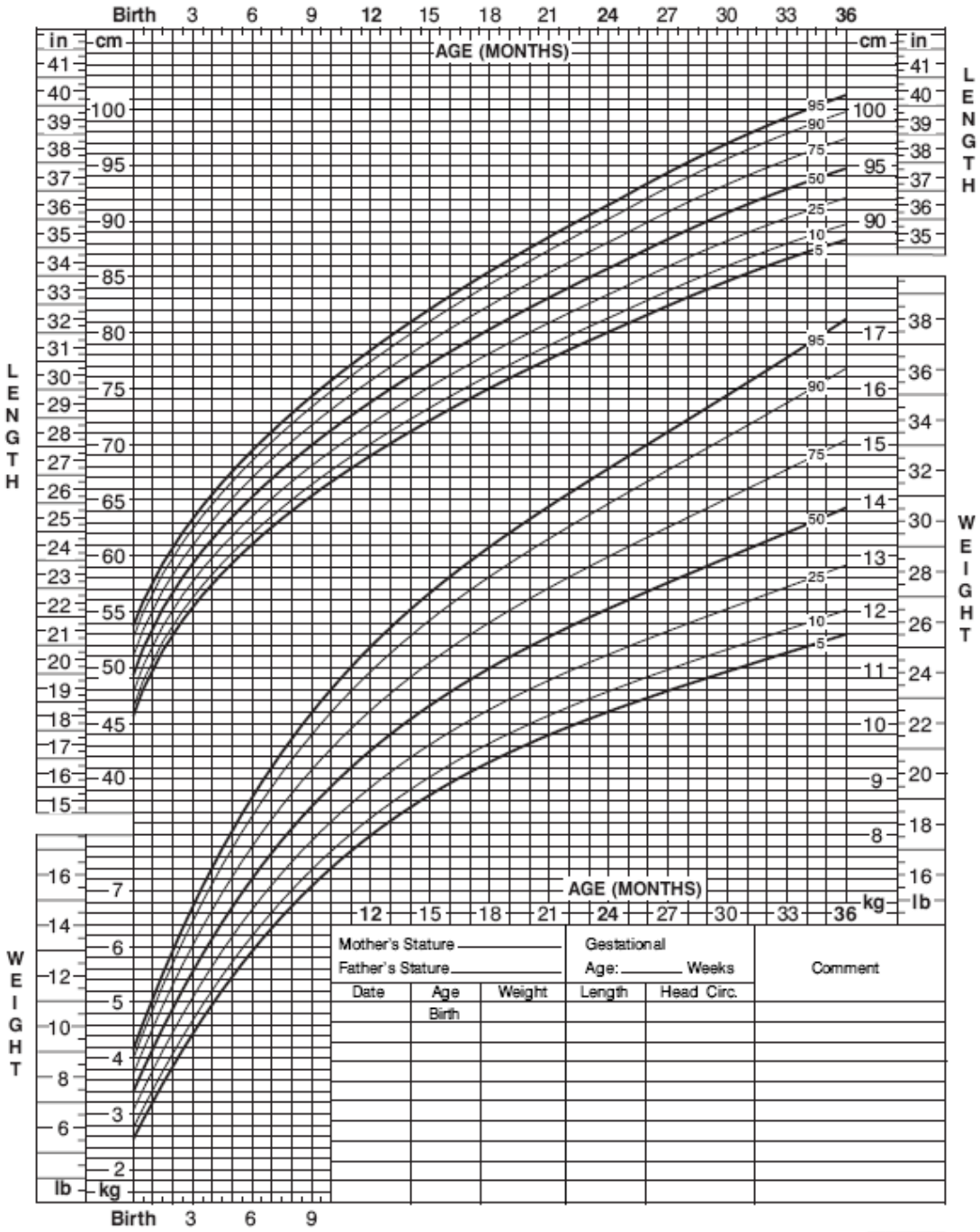

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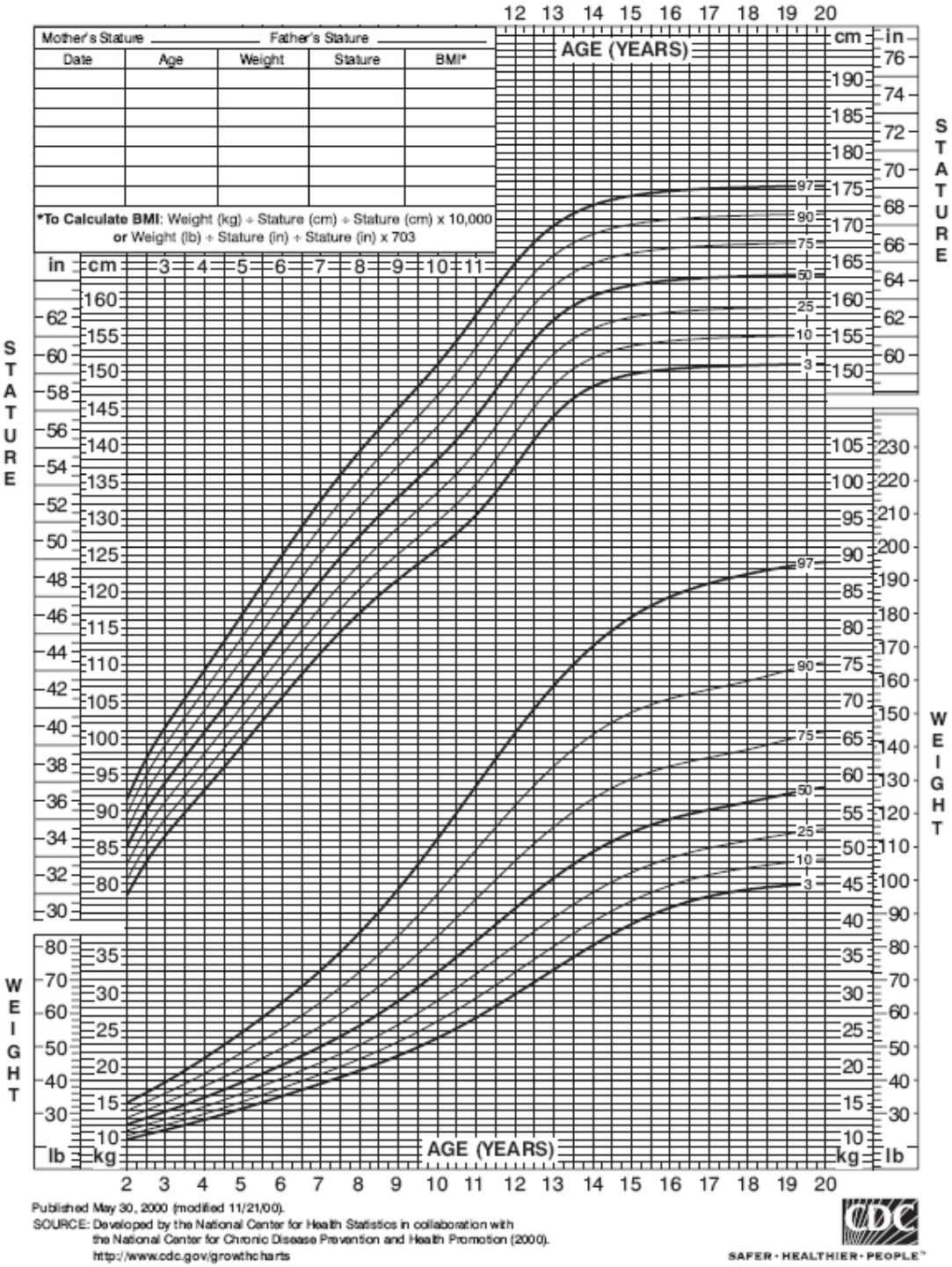

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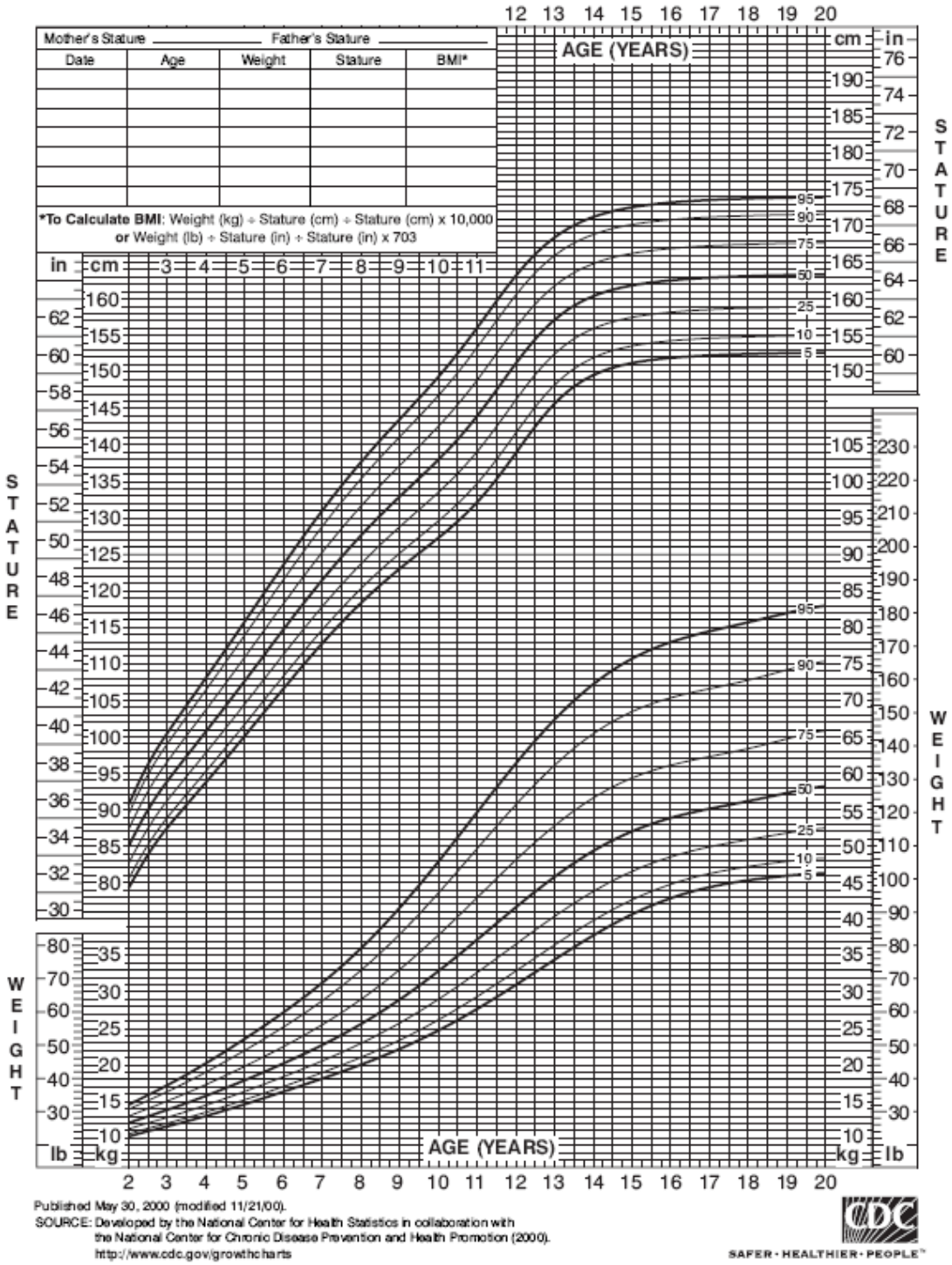

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SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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Appendix 11: Adverse Event Definitions

Listed below are guidelines for uniform reporting of adverse events related to the study valve. The definitions and categorization of event types are consistent with those recommended by Akins *et al.*[25] The DSMB will review and adjudicate adverse events according to these reporting guidelines.

Death

All deaths will be reported and categorized as either 'valve related', 'other cardiac related', or 'other cause' as defined below.

Valve-Related:

Death due to any of the following events involving the study valve: structural valvular deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, endocarditis, or reintervention. Sudden, unexplained deaths of which the cause or relationship has not been determined by clinical investigation or autopsy findings are considered valve related.

Other Cardiac:

Death resulting from cardiac causes, excluding valve-related death. Examples include congestive heart failure, acute myocardial infarction, and documented fatal arrhythmias.

Other Cause:

Death due to any cause, excluding valve-related mortality or other cardiac death.

Endocarditis

Any infection involving the study valve that is diagnosed according to Modified Duke Criteria[26] for endocarditis will be reported. Modified Duke Criteria are defined as follows:

1. Definite Infective Endocarditis

   Definite infective endocarditis is defined by pathologic criteria or clinical criteria as defined below. The presence of both pathologic and clinical criteria is not necessary to meet the definition of definite infective endocarditis.

   a. Pathologic Criteria

i. Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
ii. Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

b. Clinical Criteria
i. 2 major* criteria; or
ii. 1 major* criterion and 3 minor** criteria; or
iii. 5 minor** criteria

2. Possible Infective Endocarditis
a. 1 major* criterion and 1 minor** criterion; or
b. 3 minor** criteria

3. Rejected
a. Firm alternate diagnosis explaining evidence of infective endocarditis; or
b. Resolution of infective endocarditis syndrome with antibiotic therapy for ≤ 4 days; or
c. No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
d. Does not meet criteria for possible endocarditis, as above

*Duke Major Criteria:

1. Blood culture positive for infective endocarditis
a. Typical microorganisms consistent with IE from 2 separate cultures:
i. Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or
ii. Community-acquired enterococci, in the absence of a primary focus, or
b. Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows:
i. At least 2 positive cultures of blood samples drawn > 12 hours apart; or
ii. All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 hour apart)
c. Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer > 1:800

2. Evidence of endocardial involvement

3. Echocardiogram positive for infective endocarditis (TEE recommended), defined as follows:

a. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
b. Abscess; or
c. New partial dehiscense of prosthetic valve

4. New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

**Duke Minor Criteria:

1. Predisposition, predisposing heart condition or injection drug use

2. Fever, temperature > 38°C

3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions

4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above (excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with infective endocarditis

Endocarditis meeting the Duke definitions for 'definite' or 'possible' will be reported.

Positive blood cultures are not required for the diagnosis of study valve endocarditis. Morbidities associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak, are included under this category, and not counted in other categories of morbidity.

Hemorrhage

Any episode of major internal or external bleeding that causes death, hospitalization, pericardiocentesis, permanent injury (e.g., vision loss), or requires transfusion will be reported.

Note: A bleeding event is reportable whether or not the subject is taking anticoagulant or antiplatelet medication.

Note: Embolic stroke complicated by bleeding is classified as a neurological event under "embolism" and is not included as a separate bleeding event.

Nonstructural Dysfunction

Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the study valve or hemolysis will be reported. Nonstructural dysfunction refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction of a study valve, as diagnosed by reoperation, autopsy, or clinical investigation.

Examples of nonstructural dysfunction include: entrapment by pannus, tissue, or suture; paravalvular leak; inappropriate sizing or positioning; residual leak or obstruction after valve implantation or repair; and clinically significant intravascular hemolytic anemia. More than mild recurrent or residual mitral regurgitation after surgical or percutaneous interventional valve procedures (coronary sinus interventions, direct reparative methods, or other methods aimed at achieving ventricular remodeling) is nonstructural dysfunction, unless there is disruption of the valve components themselves, which would then be structural deterioration.

Sudden or progressive dysfunction or deterioration of the study valve may be structural, nonstructural, or both as determined by reoperation, autopsy, or clinical investigation.

Reoperation

Reoperation is any operation that repairs, alters or replaces the study valve. The reasons for reoperation are to be reported and may include reasons other than valve-related morbidity, such as recall, excessive noise, or incidental or prophylactic removal.

Thrombolytic or catheter-aided therapy of valve-related morbidity is not considered reoperation; however, the morbid event that prompted the intervention should be reported.

Structural Valve Deterioration

Dysfunction or deterioration involving the study valve (exclusive of infection or thrombosis), as determined by reoperation, autopsy, or clinical investigation will be reported. Structural valve deterioration refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components (e.g., leaflets) of the study valve.

Thromboembolism

Any thromboembolic event that occurs in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness is completely reversed) will be reported as valve-related. Thromboembolic events occurring during the procedure will be reviewed and adjudicated by the DSMB to determine if the event is valve or procedure related. Subsets of thromboembolic events are:

Neurologic:

A neurologic thromboembolism is one that results in a central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia. Types of neurologic events are:

- Stroke: A prolonged (>72 hours) or permanent neurologic deficit that is usually associated with abnormal results of magnetic resonance imaging or computed tomographic scans. Subjects with minimal, atypical, or protean symptoms that lead to radiographic imaging demonstrating an acute ischemic event are considered to have sustained a stroke.

- Transient Ischemic Attack (TIA): Fully reversible symptoms of short duration. If radiographic imaging demonstrates an acute central neurologic lesion ("cerebral infarction with transient symptoms"), however, such subjects are reclassified as having sustained a stroke.

Noncerebral:

A thromboembolism documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a peripheral artery.

Valvular Thrombosis

Any thrombus not caused by infection attached to or near the study valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valvular thrombosis found at autopsy in a subject whose cause of death was not valve related or found at operation for an unrelated indication should also be counted as valvular thrombosis.