



eCRF Completion Guidelines



CLN0021

A Prospective Multicenter Open-label Randomized Controlled Trial of Agili-C™ vs. Surgical Standard of Care (SSOC) for the Treatment of Joint Surface Lesions of the Knee

Protocol Version: CLN0021-US Rev. 2 Sep 1, 2017

Prepared by:

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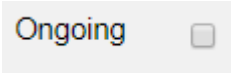

Prepared for:



CartiHeal

1. GENERAL INSTRUCTIONS

Source Documents	<p>Ensure data entries in Medidata Rave are consistent with the source data. All source documentation should be stored at the site.</p>
Dates	<p>At each visit, please enter Date of Visit prior to entering any other data.</p> <p>In case the visit was not performed – complete only the <u>Date of Visit</u> form.</p> <p>Record all dates in DD-MMM-YYYY format.</p> <p>Some forms allow "Unknown" to be entered for either day or month.</p> <ul style="list-style-type: none"> • If only the month and year are known, enter the date as: 'UN-mmm-yyyy'. • If only the year is known, enter the date as: 'UN-UNK-yyyy'. <p>Rave does not accept UNK for Year value.</p> <p>In cases year is unknown, leave the date field blank and record a comment clarifying the missing data.</p> <p>If UN/UNK values are not accepted, full date is required.</p> <p>Follow-Up X-Ray and MRI have to be performed within the visit time window.</p>
Time	<p>Enter Time in 24-hour format e.g. 1:00 PM should be entered as 13:00</p> <p>Rave does not accept UN values for Time. If the time is unknown, the field should be left blank and a relevant comment should clarify the reason for missing data.</p>
Dynamic Data Base	<p>Complete all forms in the order they appear within the folder.</p> <p>All forms within a visit are required to be completed.</p> <p>After saving a form make sure no data is missing, since there are fields that become visible only after a certain data is entered and saved.</p>

<p>Use of Unknown, Not Done or Not Applicable</p>	<p>Every effort must be made to obtain all the required data.</p> <p>In case the information is not available:</p> <p><u>For text/numeric fields, enter one of the following missing codes:</u></p> <ul style="list-style-type: none"> • ND – Not Done • NA – Not Applicable • UN - Unknown <p><u>For selection fields (Radio Button/Dropdown Lists):</u></p> <p>Leave the field blank. In most cases a query will pop up requiring an explanation for the missing data.</p> <p>For every missing data point – a clarifying comment should be recorded (see comments section below).</p> <p>All forms within a visit are required to be completed.</p> <p>In case visit was not performed – only the Date of Visit should be completed. The rest of the forms within the visit should be left blank.</p>
<p>Radio Button</p>	<p>Used when only one response can be selected from a limited number of responses.</p> <p>Example:</p> <div data-bbox="478 1397 1276 1473"> <p>Is the patient symptomatic in both knees? <input type="radio"/> Yes <input type="radio"/> No</p> </div>
<p>Dropdown Lists</p>	<p>Used when only one response can be selected from a list of responses.</p> <p>Example:</p> <div data-bbox="478 1688 1436 1845"> <p>What is the assigned Treatment based on randomization and algorithm?</p> <div> <div>...</div> <div> Agili-C SSOC - Microfracture SSOC - Debridement </div> </div> </div>

<p>Check box</p>	<p>Used when more than one response can be selected from a list of responses or as a check mark for a single option (e.g. 'Ongoing' in CM form) or to trigger an action (e.g. Add form at Unscheduled visit).</p> <p>Examples:</p> <div data-bbox="480 539 711 611">  </div> <p>Was any of the following injected into the treated knee since the last visit?</p> <p>If Yes, please check all that apply and update the Adverse Events log and the Concomitant Medications log accordingly:</p> <div data-bbox="480 719 1445 898"> <table> <tr> <td>HA</td> <td><input type="checkbox"/></td> </tr> <tr> <td>PRP</td> <td><input type="checkbox"/></td> </tr> <tr> <td>Stem Cells</td> <td><input type="checkbox"/></td> </tr> <tr> <td>Steroids</td> <td><input type="checkbox"/></td> </tr> </table> </div>	HA	<input type="checkbox"/>	PRP	<input type="checkbox"/>	Stem Cells	<input type="checkbox"/>	Steroids	<input type="checkbox"/>
HA	<input type="checkbox"/>								
PRP	<input type="checkbox"/>								
Stem Cells	<input type="checkbox"/>								
Steroids	<input type="checkbox"/>								
<p>Hidden fields</p>	<p>In some forms there are hidden fields which appearance is triggered by specific answers after the form is saved. Make sure all questions are answered properly before moving to the next eCRF page.</p>								
<p>Sticky Notes</p> <div data-bbox="140 1238 177 1272">  </div>	<p>Sticky Notes are used for reminders and for communicating with another user.</p> <p>Sticky notifications raised upon data entry are usually a reminder to the user (site user/CRA) to perform additional actions.</p> <p>Once the requested action was completed, use ' Acknowledge' to remove the sticky note from your task summary.</p>								

<p>Data queries</p> 	<p>A query is a question about a data point on a form that can be triggered manually by the CRA/Data Management, or automatically by the system.</p> <p>The Study Coordinator is able to see a list of all open queries in 'Task Summary' on the main page. It is possible to navigate to the query from the 'Task Summary'.</p> <p>All queries-associated activities (i.e. Open, Answer, Cancel, Close, Re-query) are recorded in the audit trail.</p> <p>◆  – Non conformant data:</p> <p>Data is not compatible with the assigned field format and must be changed. The field will be marked in red, no message will be displayed.</p> <p>◆ Automatic queries within a form should be addressed before moving to the next eCRF for that visit.</p> <p>◆ To close a query, either the data point in question should be changed or a response should be recorded in the Query Resolution textbox provided within the query.</p> <p>If applicable, please use the following responses:</p> <ul style="list-style-type: none"> - "Original value is correct" – in case data was queried, yet, after verification with source documents should not be changed. - "Changed data per query" – in case the data in question was updated. - "Data is not in patient records" – in case the required data cannot be obtained. <p>Use free text for all other cases.</p> <p>◆ Data Management will review the entered data and generate Manual queries if needed.</p> <p>◆ When responding to data queries, please make sure that in addition to entering a response in the Query Resolution textbox the relevant data fields were updated/completed accordingly. (Entering the updated data value in the Query Resolution textbox will not update the discrepant values in the form, and the field in question will have to be re-queried.)</p>
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Comments

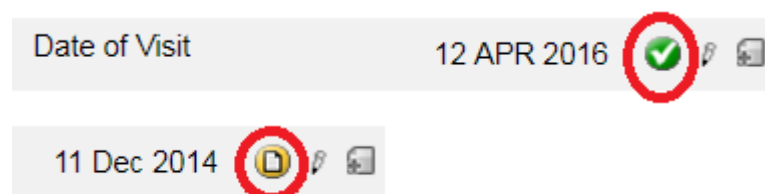
The purpose of a comment is to provide additional information/clarification for a specific data point when no designated field for this information is found in the eCRF.

For example:

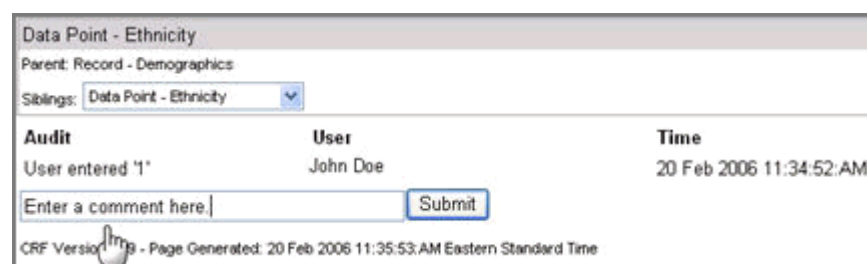
For a missing data point, add a comment that clarifies the reason for the missing data.

A comment can be recorded for any data field.

To add a comment, navigate to the audit trail for a data point:

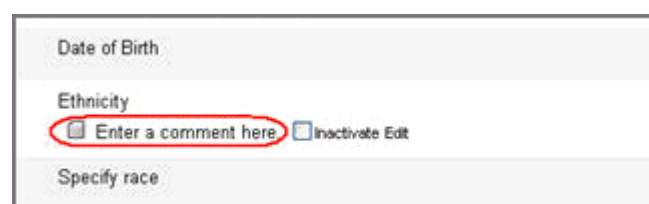


Enter a comment in the text box:



Click **Submit**.

The annotation displays below the data field on the form.



To edit the annotation, click **Edit** next to the annotation on the form page.

Log Forms**The following forms are Log Forms:**

- Adverse Events & Serious Adverse Events
- Concomitant Medications
- Medical History

Adding Log Lines

1. Enter the necessary data in the Log form and click Save → The log form displays log line 1 of 1.
2. Click Add a new Log line.

#	Description	Start	Stop	Continuing
1	abaababbaba	12 Jan 2006	15 Jan 2006	No
Add a new Log line Inactivate				
Printable Version View PDF Icon Key				

A new log line appears.

Inactivating Log Lines

After a log line is successfully saved, it can be inactivated. This may be done if a line is entered in error for a subject, among other reasons

NOTE: Log lines cannot be deleted, they can only be inactivated

1. Navigate to the Log form.
2. Click Inactivate on the complete view of the log form.

#	Description	Start	Stop	Continuing	SAE?
1	abaababbaba	12 Jan 2006	15 Jan 2006	No	No
2	xyxyxyxyx	16 Jan 2006	17 Jan 2006	Yes	No
Add a new Log line Inactivate					
Printable Version View PDF Icon Key					
CRF Version 91 - Page Generated Feb 2006 02:24:34 PM East					

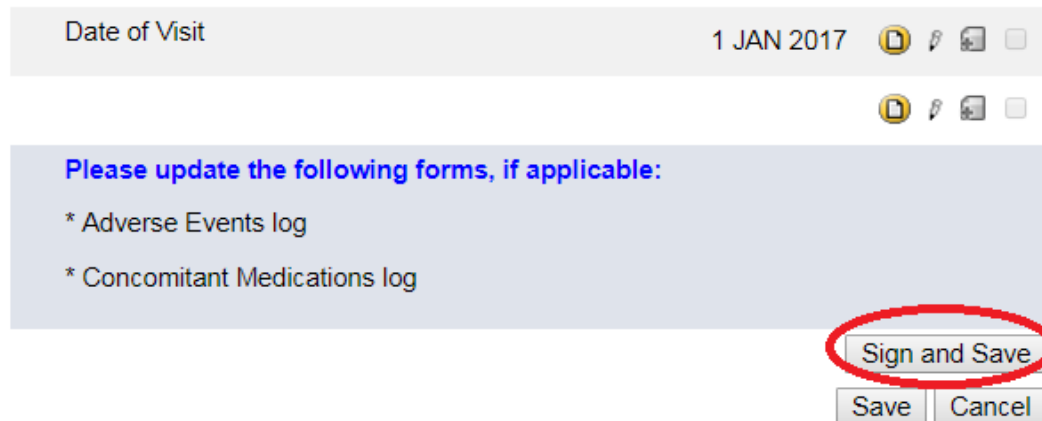
A dropdown with all log lines appears.

#	Description	Start	Stop	Continuing	SAE?
1	abaababbaba	12 Jan 2006	15 Jan 2006	No	No
2	xyxyxyxyx	16 Jan 2006	17 Jan 2006	Yes	No
<div> ... Inactivate Cancel </div>					

Select the line that you want to inactivate, and, if applicable, enter the reason for the inactivation → Click **Inactivate**.

2. INVESTIGATOR'S ELECTRONIC SIGNATURE

Upon completion of Sponsor's review of the Subject's casebook the Investigator is expected to electronically sign the forms.



Date of Visit 1 JAN 2017

Please update the following forms, if applicable:

- * Adverse Events log
- * Concomitant Medications log

Sign and Save

Save Cancel

The electronic signature should be applied with the appropriate **user name** and **password**.

3. ADVERSE EVENTS & SERIOUS ADVERSE EVENTS LOG

The Adverse Events Log can be accessed via the Adverse Events folder at any stage of the study.

The Adverse Events Log should be updated whenever an Adverse Event occurs during the study.

To add a new Adverse Event use the '**Add a new Log**' option.

(For a detailed explanation, see the '**Log Forms**' section under 'GENERAL INSTRUCTIONS')

To inactivate an entered line use the '**Inactivate**' option.

(For a detailed explanation, see the '**Log Forms**' section under 'GENERAL INSTRUCTIONS')

The following should be reported as Adverse Event:

- Untoward medical conditions or signs or symptoms that were absent before starting study treatment.
- Untoward medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory findings
- Clinical signs or symptoms that require therapy

Event which was present pre-study is not considered as an adverse event unless it has worsened since the enrollment to the study.

An SAE is an Adverse Event that:

- Led to a death
- Led to a serious deterioration in the health of the subject that:
- Resulted in a life-threatening illness or injury.
- Resulted in a permanent impairment of a body structure or a body function.
- Required in-patient hospitalization or prolongation of existing hospitalization.
- Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and hospitalizations for treatment of non-adverse events (e.g. cosmetic surgery or diagnostic procedure) are not considered serious adverse events.

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Event Start Date (Initial)	If the exact date is unknown, UN can be entered for the unknown day, and UNK can be selected for the unknown month.
Date of Follow-Up & Follow-Up narrative	Each time the Adverse Event record is updated with new information, the appropriate 'Follow-Up Date' & 'Follow-Up Narrative' fields should be updated.
Event End Date (Final)	If the event is Ongoing, this field should be left empty.
Please select the SINGLE term that BEST describes the adverse event	<p><u>One option</u> should be selected from the list.</p> <p>If there is no option in the list that matches the Adverse Event description, 'Other' should be selected and a specification must be entered (free text). NOTE: Standard medical terminology should be used whenever possible. The full medical term should be recorded. No abbreviations are allowed.</p>
Please mark ALL OTHER symptoms related to the event	<p>All the relevant symptoms should be checked.</p> <p>For symptoms that are not listed in the form, a specification should be entered under 'Other symptoms, please specify' (free text).</p>
What is the intensity or severity of the Adverse Event	<p>One option should be selected from the dropdown list.</p> <p><u>Mild</u>: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.</p> <p><u>Moderate</u>: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.</p> <p><u>Severe</u>: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.</p>

Relatedness to study device and/or tool-set or to study procedure	<p>The most relevant description should be selected from the dropdown list.</p> <p><u>Unrelated</u> – The temporal sequence of the AE onset relative to treatment by the investigational device/SSOC is not reasonable. OR There is another obvious cause of the AE .</p> <p><u>Unlikely related</u> – The relationship with the use of the device/SSOC can be reasonably explained by another cause, but additional information may be obtained .</p> <p><u>Possibly related</u> – The relationship with the use of the investigational device/SSOC is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent clinical condition or/and an effect of another device, or treatment .</p> <p><u>Probably related</u> – The relationship with the use of the investigational device/SSOC seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained .</p> <p><u>Related</u> – The AE can be explained only by the use of the investigational device/SSOC .</p> <p><u>Uncertain</u> – The relationship between the AE and the device is uncertain.</p>
Any treatment or action taken?	<p>If the answer is 'Yes', sections (a), (b) & (c) should be answered as well.</p>
(a) Any surgery performed in the operated knee?	<p>If 'Yes':</p> <ol style="list-style-type: none"> 1. A specification should be entered (in free text) 2. An Unscheduled Visit should be added (see instructions below, under the 'UNSCHEDULED VISIT' section) → the 'Cartilage Repair Assessment' form should be updated (within the 'Unscheduled visit' folder). 3. All question under section (a) should be answered ("Any action taken regarding study device?" and questions regarding Biopsy) <p>If 'No':</p> <p>All question under section (a) should be left empty ("Any action taken regarding study device?" and questions regarding Biopsy).</p>

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Any action taken regarding study device?	If 'Yes', the next question should be answered. If 'No', the next question should be left empty.
If yes, please check the appropriate action taken	One option should be selected from the dropdown list.
In case of Surgical Intervention in the Operated Knee - was a Biopsy or a Specimen taken?	One option should be selected from the dropdown list. If 'No', sections (i) and (ii) should be left empty. If 'Yes – sent to External Lab' – section (i) ('External Lab') should be answered. If 'Yes – sent to Local Lab' – section (ii) ('Local Lab') should be answered. If 'Yes – sent to both...' – both sections (i) & (ii) should be answered.
(b) Any Intra-articular injection in the operated knee? (Excluding knee aspiration)	If YES – check all that apply and update the Concomitant Medications log accordingly.
(c) Other treatment or action taken?	If Yes a specification should be entered (in free text) and the Concomitant Medications log should be updated accordingly.
Outcome of Adverse Event	One option should be selected from the dropdown list. If the Outcome = Death, ' Death ' form will be added to the Adverse Events folder, and should be updated accordingly.
Does the Adverse Event meet any of the following definitions of a Serious Adverse Event?	Check all that apply. Do not confuse with Severe Adverse Event. If 'Led to death' is checked, ' Death form ' is added to the ' Adverse Events ' folder and should be updated accordingly.
Please describe the event and all relevant clinical findings	Free text.

3.1. DEATH FORM

Date of Death	Full date is required.
Time of Death	Enter Time in 24-hour format.
Primary Cause of Death	Free text. The specified reason must be consistent with the Adverse Events log.
Secondary Cause of Death	If applicable.

4. CONCOMITANT MEDICATIONS

The Concomitant Medications Log can be accessed via the Concomitant Medications folder at any stage of the study.

The Concomitant Medications log aims to capture any medication received by the patient with regard to the knee condition.

Reported medications should include all analgesic and anti-inflammatory medications received within **3 months** before screening as well as any other medications received due to the knee condition in the opinion of the PI.

Please do NOT report the following medications:

- Anesthetic agents used for surgery
- Antiemetics (e.g. Ondansetron and similar agents (
- Chlorhexidine (topical wash or oral (
- Eye drops (for moistening or tear replacement (
- H2 Blockers (e.g., Ranitidine, Famotidine, Cimetidine (
- Heparin Sq (if used for DVT prophylaxis (
- Lovenox Sq (if used for DVT prophylaxis (
- Insulin, if protocolized for ICU patients with elevated blood glucose.
ALL other uses of Insulin or other Hypoglycemic Agents are to be recorded .
- IV Solutions and Electrolytes
- Magic mouthwash
- Pain medications (e.g. Fentanyl, Morphine, Dilaudid). NSAID use is to be recorded .
- Proton Pump Inhibitors (e.g., Omeprazole, Pantoprazole, lansoprazole, Esomeprazole (
- Red Blood Cell transfusions (Platelet and FFP transfusions are to be recorded (
- Sedatives or Anti-anxiety drugs (e.g. Benzodiazepams, Midazolam, Propofol (
- Sevelamer
- Skin ointments or creams
- Sleeping agents (e.g. Ambien, Lunesta, Sonata, Melatonin (
- Stool Softeners (e.g. Colace, Dulcolax, etc (
- Total Parenteral Nutrition including intravenous lipids
- Tylenol (either for pain or fever (
- Vitamins and Supplements (including oral supplements such as Calcium, Magnesium or Potassium supplements for Hypokalemia)

Use a separate line for each unique medication.

To add a new Medication use the '**Add a new Log**' option.

(For a detailed explanation, see the '**Log Forms**' section under 'GENERAL INSTRUCTIONS')

To inactivate an entered line use the '**Inactivate**' option.

(For a detailed explanation, see the '**Log Forms**' section under 'GENERAL INSTRUCTIONS')

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Name (Generic)	<p>The full medication generic name or trade name should be entered (preferably generic). If the full name is unknown, all the generic ingredients should be recorded in a single record.</p> <p>A new entry is required for any change of Dose/Frequency/Route during the study.</p>
Steroids?	Yes / No
Indication	<p>All indications for therapy must be consistent with the MH and/or AE logs, or with the Standard of Care for the knee condition.</p> <p>If a medication is given for more than one reason, only the primary reason should be recorded.</p>
Start Date	If the exact date is unknown, UN can be entered for the unknown day, and UNK can be selected for the unknown month.
End Date	If the medication is Ongoing, this field should be left empty.
Ongoing	If 'Ongoing' is checked, Stop Date should be empty.
Dose	Administration dose per <u>single administration</u> (numeric values only)
Units	<p>One option should be selected from the dropdown list.</p> <p>If 'Other' is selected, a specification is required.</p>
Frequency	<p>Frequency of a single dose administration.</p> <p>One option should be selected from the dropdown list.</p> <p>If 'Other' is selected, a specification is required.</p>
Route	<p>One option should be selected from the dropdown list.</p> <p>If 'Other' is selected, a specification is required.</p>

5. SCREENING VISIT

5.1. NEW SUBJECT– PRIMARY FORM

Subject initials	Record 2 or 3 letters of the subject's initials (AA / AAA). NOTE that once the initials are entered and saved they cannot be changed.
Informed Consent	Informed consent must be obtained on or before the Screening visit date and on or before the date of any study related procedures performance as recorded in the subject's file.
Has the subject received a written and oral explanation of the study?	Tick the checkbox for 'Yes'.
Has the subject received a copy of the signed Informed Consent Form?	Tick the checkbox for 'Yes'.

5.2. DEMOGRAPHICS

Date of birth	Patient's full date of birth (DD-MMM-YYYY). No option for partial data in this field (unknown day /month).
Age	The age is automatically calculated based on Date of Birth and Date of Informed Consent.
Ethnicity	<u>Hispanic or Latino</u> : A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, “Spanish origin,” can be used in addition to “Hispanic or Latino”.

Race	<p><u>American Indian or Alaska Native</u>: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.</p> <p><u>Asian</u>: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.</p> <p><u>Black or African American</u>: A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American”.</p> <p><u>Native Hawaiian or Other Pacific Islander</u>: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.</p> <p><u>White</u>: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.</p>
Height	Enter Height in centimeters or inches and select the appropriate units from the dropdown list.
Weight	Enter Weight in kilograms or pounds and select the appropriate units from the dropdown list.
BMI	The BMI is calculated automatically, based on Height and Weight.

5.3. BASELINE DATA

Is the patient symptomatic in both knees?	<p>If the answer is 'Yes', the following question will be added upon the form saving:</p> <p>Which knee is more symptomatic?</p>
Which knee is more symptomatic?	<p>The question is added only if 'Is the patient symptomatic in both knees?' is answered as 'Yes'.</p> <p>Only one option should be selected: Right / Left / Equally symptomatic</p>
Which knee will be treated in the study?	<p>If the 'more symptomatic knee' differs from the 'treated knee', a specification field will be added upon the form saving.</p>

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Please specify the reason why the more symptomatic knee is not the treated knee	<p>The question is added only if the 'more symptomatic knee' differs from the 'treated knee'.</p> <p>The reason should be entered in free text.</p>
Does the subject have an MRI not older than 1 year prior to Screening date?	<p>The subject must have an MRI not older than 1 year prior to Screening date.</p>
Does the subject have a standing X-Ray (AP and Lateral) not older than 1 year prior to Screening date?	<p>The subject must have an X-Ray (AP and Lateral) not older than 1 year prior to Screening date.</p>
Does the subject smoke cigarettes?	<p>One option should be selected from the dropdown list.</p>
KOOS PAIN SCALE	<p>For each question (P1 to P9) one option should be selected from the dropdown list.</p>
KOOS Pain Score	<p>The score is calculated automatically once the form is saved.</p> <p>In case there is missing data, a maximum of 2 items are allowed to be omitted in order for the score to be considered valid.</p> <p>If the score is less than 20 or more than 65, the subject must be excluded from the study and the 'End of Study' form should be updated.</p>
Is the subject taking any medications?	<p>If 'Yes', the Concomitant Medications log should be updated accordingly.</p>
During the past 3 months, has the subject received any medications, including intra-articular injections, to treat the knee symptoms?	<p>If 'Yes', the Concomitant Medications log should be updated accordingly.</p>

5.4. MEDICAL HISTORY

'Does the subject have a medical or surgical history, current or resolved, of any of the following?' –

For each body system, one of the following options should be selected:

- **Yes** – if the subject has a medical or surgical history related to the body system.
- **No** – no medical or surgical history related to the body system.
- **Unknown**

In case the answer is 'Yes':

1. A specification should be provided under: **'If Yes, please specify'**
2. Either **'Current'** or **'Resolved'** should be selected.

If the answer is **'No'** or **'Unknown'**, these two fields should be left empty.

NOTE that the pre-specified Body Systems should NOT be changed.

In case the subject has a medical history in a body system that is not specified in the list, a new line should be added via **'Add a new Log line'**. (For a detailed explanation, see the **'Log Forms'** section under 'GENERAL INSTRUCTIONS')

To inactivate an entered line use the **'Inactivate'** option.

(For a detailed explanation, see the **'Log Forms'** section under 'GENERAL INSTRUCTIONS')

NOTE that the pre-specified line should NOT be inactivated.

5.5. IKDC KNEE EXAMINATION FORM 2000 - SURGEON'S PART

Generalized Laxity Alignment Patella Position Patella Subluxation/Dislocation	For each question, one option should be selected.
Range of Motion (Ext/Flex)	Record <u>numeric</u> values for Hyperextension / Zero Point / Flexion . (e.g. 10 degrees of hyperextension, 150 degrees of flexion: Hyperextension=10 / Zero Point=0/ Flexion=150; 10 degrees of flexion to 150 degrees of flexion = Hyperextension=0/Zero Point=10/Flexion=150) Extension is compared to that of the normal knee.

<p>SEVEN GROUPS</p> <p>* 3. Ligament Examination</p>	<p>For each question, one option should be selected from the dropdown list.</p> <p>'Method of Assessment' should be selected: Manual / Instrumental / X-ray</p> <p>The following questions should be answered in accordance with the selected 'Method of Assessment':</p> <p>Only if Instrumented or X-Ray Examination – Δ Lachman (25° flex) (134N) (should be left empty if 'Method of Assessment' = Manual)</p> <p>Only if Manual Examination – Δ Lachman (25° flex) manual max: (should be left empty if 'Method of Assessment' = Instrumental or X-Ray)</p>
<p>IKDC Surgeon's Part Score</p>	<p>The score is calculated automatically once the form is saved.</p> <p>If the score is C or D, the subject must be excluded from the study and the 'End of Study' form should be updated.</p>

5.6. ICRS KNEE SURGERY HISTORY REGISTRATION – SURGEON'S PART

<p>Did the subject have any previous surgeries in the Index Knee (Knee Under Study)?</p>	<p>If the answered as 'Yes', a new form is added to the Screening Visit folder: ICRS Knee Surgery History Registration - INDEX KNEE</p>
<p>Did the subject have any previous surgeries in the Other Knee?</p>	<p>If the answered as 'Yes', a new form is added to the Screening Visit folder: ICRS Knee Surgery History Registration - OTHER KNEE</p>

5.6.1. ICRS KNEE SURGERY HISTORY REGISTRATION – INDEX KNEE (if applicable)**5.6.2. ICRS KNEE SURGERY HISTORY REGISTRATION – OTHER KNEE (if applicable)**

Meniscal surgery Ligament Surgery Extensor Mechanism Surgery Patellofemoral Surgery Cartilage Resurfacing and Reconstructive Surgery	<p>All the relevant Surgery Categories should be checked.</p> <p>Once the form is saved, for each surgery category additional fields will be added specifying the surgery sub-categories.</p> <p>Example:</p> <div style="border: 1px solid #ccc; padding: 5px; margin: 10px 0;"> <p>1 Meniscal surgery <input checked="" type="checkbox"/></p> <p>1.1 Medial Meniscal Surgery <input checked="" type="checkbox"/></p> <p>1.2 Lateral Meniscal Surgery <input type="checkbox"/></p> </div> <p>Make sure all the required fields are updated.</p> <p style="color: red;">For each checked surgery category make sure that at least one sub-category was checked.</p>
Other Type of Technique (specify)	Free text specification should be entered.

5.7. INCLUSION/EXCLUSION CRITERIA

For a subject to be eligible for the study, all Inclusion Criteria must be answered as 'Yes', and all Exclusion Criteria must be answered as 'No'.

* EXCEPTION: **for male subjects only**, Exclusion #19 must be answered as 'Not applicable'.

If one or more of the criteria are not met, the subject must be excluded from the study and the '**End of Study**' form should be updated.

Once all Inclusion/Exclusion Criteria are answered appropriately (i.e. all criteria are met) additional forms will be added to the Screening Visit folder.

5.8. KOOS QUESTIONNAIRE - PATIENT'S PART (BASELINE - W/O PAIN SUBSCALE)

For each question, one option should be selected from the dropdown list.

All questions must be answered.

NOTE that the KOOS Questionnaire at Screening Visit does not contain the KOOS Pain Subscale, since it was already captured within the 'Baseline Data' form.

Scores

The scores are automatically calculated for each subscale once the form is saved.

In case there is missing data, a maximum of 2 items are allowed to be omitted in order for the score to be considered valid.

Overall Score

The overall score is calculated automatically once the form is saved, based on all five subscales, including the KOOS Pain Subscale from ('Baseline Data' form).

5.9. SF-12 VERSION 2 HEALTH SURVEY

For each question, one option should be selected from the dropdown list.

All questions must be answered.

SF-12 Score

The SF-12 Score is calculated externally and is to be entered at a later stage.

5.10. ICRS – CARTILAGE INJURY STANDARD EVALUATION FORM 2000 PATIENT'S PART

Involved (Treated) Knee	Copied from Baseline Data once the form is saved.
Opposite Knee	One option should be selected.
Onset of Symptoms Date	If the exact date is unknown, UN can be entered for the unknown day, and UNK can be selected for the unknown month.
Onset of Symptoms Nature	One option should be selected.
Please select Type of Activity	One option should be selected from the dropdown list.

Please specify (if applicable)	The type of activity can be specified in free text if applicable.
Please select the activity level before the injury.	One option should be selected from the dropdown list.
Please select the activity level after the injury.	One option should be selected from the dropdown list.
Functional Status – Pre-injury	One option should be selected from the dropdown list.
Functional Status – Just Prior to Surgery	One option should be selected from the dropdown list indicating subject's present functional status.
Functional Status – Present Activity Level	Automatically copied from ' Just Prior to Surgery ' once the form is saved.

5.11. IKDC SUBJECTIVE KNEE EVALUATION

For each question, one option should be selected from the dropdown list.

All questions must be answered.

IKDC Patient's Part Score

The score is automatically calculated once the form is saved.

In case there is missing data, a maximum of 2 items are allowed to be omitted in order for the score to be considered valid.

5.12. TEGNER ACTIVITY SCORE

For each question, one option should be selected from the dropdown list.

All questions must be answered.

5.13. BASELINE STANDING X-RAY (AP & LATERAL) AND MRI

Was a Standing X-Ray (AP and Lateral) uploaded to the server?	Tick the checkbox for 'Yes'.
The date when X-Ray was uploaded to the server	No partial date is allowed.
Was an MRI uploaded to the server?	Tick the checkbox for 'Yes'.
The date when MRI was uploaded to the server	No partial date is allowed.

Once the form is saved, additional questions will appear – will be answered off-site:

K/L grade according to the Center Lab	<p>One option should be selected from the dropdown list.</p> <p>If the K/L grade is =4, the subject must be excluded from the study and the 'End of Study' form should be updated.</p>
Evaluation of Exclusion Criteria based on MRI and X-Ray	<p>For a subject to be eligible for the study, all Exclusion Criteria must be answered as 'No' or 'Not able to determine'.</p> <p>If one or more of the criteria are not met, the subject must be excluded from the study and the 'End of Study' form should be updated.</p>

If all the entered data indicates subject's eligibility for the study, 'Investigator's Approval of Subject Enrollment' form will be added to the Screening Visit folder.

5.14. INVESTIGATOR'S APPROVAL OF SUBJECT ENROLLMENT


"I declare that the subject fulfills all Inclusion and Exclusion criteria, has given written informed consent and can be enrolled into the study." – must be answered as 'Yes' in order for the subject to be eligible for the study.

The form must be updated by the Investigator, under the appropriate user name and password.

<p>Once the subject's eligibility is approved by the Investigator, all the study visits will be added to the subject's matrix.</p>

6. FINAL SCREENING/PROCEDURE

**NOTE that part of the data in this folder is uploaded directly from the IWRS application.
 Once the data is uploaded, additional information will be required.**

To update the missing data, please press the 'Edit' icon at the top of the page: 

6.1. DATE OF VISIT

Please remember to update the Date of Visit (retroactively).

6.2. KNEE EVALUATION AND CONCOMITANT TREATMENT

<i>The following questions should be answered after careful assessment by visualization and palpation of the specified structures:</i>	<p>For all the following fields:</p> <p>Questions written in blue font: will be uploaded automatically from the IWRS.</p> <p>All other questions require manual data entry once the Randomization is performed.</p>
Concomitant Treatments – Were any concomitant treatments performed?	<p>Automatically uploaded from the IWRS.</p> <p>If 'Yes' – the appropriate concomitant treatments should be chosen manually.</p>
If yes, please check all that apply	<p>If 'Were any concomitant treatments performed?' = 'Yes': the appropriate concomitant treatments should be chosen manually.</p> <p>If 'Were any concomitant treatments performed?' = 'No': no concomitant treatments should be chosen.</p>
Malalignment Correction (HTO)	If checked, HTO Type and Type of Fixation should be updated.
Other, please specify	If 'Other', a specification should be provided in free text.
Inclusion and Exclusion Criteria	Automatically uploaded from the IWRS.
Untreatable Lesions – Were non-treatable lesions identified on the Medial Femoral	Automatically uploaded from the IWRS.

Condyle, Lateral Femoral Condyle and/or the Trochlea?	<p>If the answer is 'Yes', the "Untreatable Lesions" form is added to the 'Final Screening/Procedure' folder and should be updated accordingly.</p> <p>If the answer is 'No', no additional action is required.</p>
Treatable Lesions	All the data is automatically uploaded from the IWRS.

6.3. UNTREATABLE LESIONS (if applicable)

How many non- symptomatic and non -treatable cartilage lesions were identified on the Medial Femoral Condyle, Lateral Femoral Condyle and/or the Trochlea?	<p>One option should be selected from the dropdown list: 0-4</p> <p>Once number of lesions is selected additional fields will be added in accordance with the specified number.</p> <p>All the added fields are mandatory.</p>
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6.4. STUDY TREATMENT: AGILI-C / SSOC

Treated Knee	Automatically copied from Baseline Data at Screening Visit
Number of Treated Lesions	Automatically copied from 'Knee Evaluation and Concomitant Treatment' form.
Randomization Date	Automatically uploaded from the IWRS.
Randomization Time (24h)	Automatically uploaded from the IWRS.
Randomization Number	Automatically uploaded from the IWRS.
Randomization Study Arm	Automatically uploaded from the IWRS.

Treatable Lesions

The following questions should be answered in accordance with the entered number of treatable lesions (e.g. if Num. of Treatable Lesions =2 – Lesion No. 1 & Lesion No. 2 fields should be updated, while Lesion No. 3 fields should be left empty).

Lesion Location	Automatically copied from 'Knee Evaluation and Concomitant Treatment' form
ICRS Grade	Automatically copied from 'Knee Evaluation and Concomitant Treatment' form
Calculated area	Automatically copied from 'Knee Evaluation and Concomitant Treatment' form
What is the assigned Treatment based on randomization and algorithm?	Automatically uploaded from the IWRS.
Was the procedure performed according to randomization and algorithm?	Yes / No If ' No ' – a specification should be provided below, under ' If No, please specify '.

The following fields should be updated only if Randomization Study Arm = Agili-C.

If Randomization Study Arm = SSOC these fields should be left empty.

FOR AGILI-C GROUP ONLY:

In case of Agili-C, was an attempt to insert the implant(s) performed?	<p>One option should be selected from the dropdown list.</p> <p>If 'No':</p> <ul style="list-style-type: none"> • Specification should be provided. • 'How many implants are present at the end of the procedure in the lesion' should be answered as 'Not applicable' • The next questions regarding the inserted implants should be left empty. <p>If 'Yes – Implantation failed':</p> <ul style="list-style-type: none"> • 'How many implants are present at the end of the procedure in the lesion' should be answered as 'Not applicable' • The next questions regarding the inserted implants should be left empty. <p>If 'Yes – Implant(s) insertion was performed':</p> <ul style="list-style-type: none"> • 'How many implants are present at the end of the procedure in the lesion' should be answered as 1 / 2 / 3 ('Not applicable' is not an option). • The next questions regarding the inserted implants should be answered in accordance with the number of inserted implants.
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How many implants are present at the end of the procedure in the lesion?	One option should be selected. Select ' Not applicable ' only if ' In case of Agili-C, was an attempt to insert the implant(s) performed? ' = ' No ' / ' Yes – Implantation failed '
Agili-CTM Implant Serial Number	Please insert the Serial Number in the following format: XXX-XXX (3 digits number, hyphen, 3 digits number)
Implant Type	Answered automatically.
Implant Diameter	One option should be selected from the dropdown list.

In case of randomization to Agili-C: was Hyaluronic Acid (HA) applied?	Yes / No If 'Yes', a specification should be provided below, under ' If Yes, please specify which Hyaluronic Acid (HA) was used '
---	---

7. POST-PROCEDURE FOLLOW-UP

For the required procedures at each visit please refer to Appendix 1.

NOTE that not all of the questions listed below appear at every follow-up visit.

Please complete all forms within each Follow Up visit.

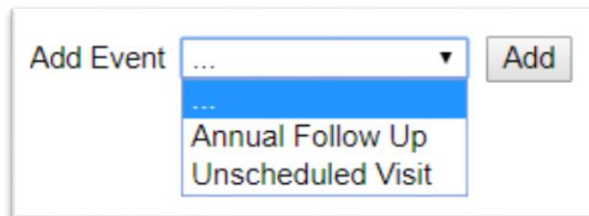
Was a Weight Bearing AP & Lateral X-ray performed?	If the answer is 'No', a specification should be provided.
Date of X-Ray	Should be answered only if 'Was a Weight Bearing AP & Lateral X-ray performed' was answered as 'Yes'.
Was the X-Ray uploaded to the server?	Should be answered only if 'Was a Weight Bearing AP & Lateral X-ray performed' was answered as 'Yes'.
Was an MRI performed according to CartiHeal Protocol?	Yes / No
Date of MRI	Should be answered only if 'Was an MRI performed according to CartiHeal Protocol?' was answered as 'Yes'.
Was the MRI uploaded to the server?	Should be answered only if 'Was an MRI performed according to CartiHeal Protocol?' was answered as 'Yes'.
Did the subject experience any new Adverse Event since the last visit?	If 'Yes', the Adverse Events log should be updated accordingly.
Was there a change in the subject's medication regimen since the last visit?	If 'Yes', the Concomitant Medications log should be updated accordingly. Record only NSAID's, anti-inflammatory and prescription medications.
Was any of the following injected into the treated knee since the last visit?	If 'Yes': <ul style="list-style-type: none"> The appropriate Intra-Articular Injection types should be selected. Adverse Events and Concomitant Medications logs should be updated accordingly.
Was any of the following procedures performed on the treated knee since the last visit?	If 'Yes': <ul style="list-style-type: none"> The appropriate Procedure types should be selected. Adverse Events log should be updated accordingly.
Has the subject followed the recommended rehabilitation process?	If the answer is 'No', a specification should be provided.

8. ANNUAL POST-24 MONTHS VISITS

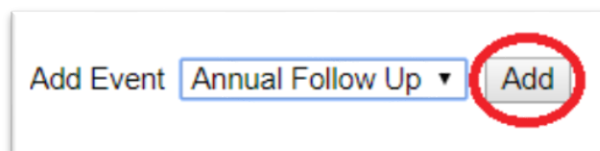
Please complete all forms within each Annual Follow Up visit.

For the required procedures at each visit please refer to Appendix 1.

To add an Annual Follow-Up Visit use the 'Add Event' button at the subject level tab:

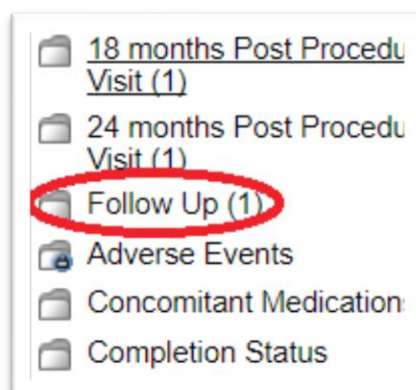


A screenshot of the 'Add Event' dropdown menu. The dropdown is open, showing three options: '...', 'Annual Follow Up', and 'Unscheduled Visit'. The 'Add' button is visible to the right of the dropdown.



A screenshot of the 'Add Event' dropdown menu. The dropdown is open, showing three options: '...', 'Annual Follow Up', and 'Unscheduled Visit'. The 'Annual Follow Up' option is selected. The 'Add' button is circled in red.

The Annual Follow-Up folder will appear after '24 months Post Procedure Visit':



A screenshot of the subject level tab showing a list of folders. The folders are: '18 months Post Procedure Visit (1)', '24 months Post Procedure Visit (1)', 'Follow Up (1)', 'Adverse Events', 'Concomitant Medication', and 'Completion Status'. The 'Follow Up (1)' folder is circled in red.

9. UNSCHEDULED VISIT

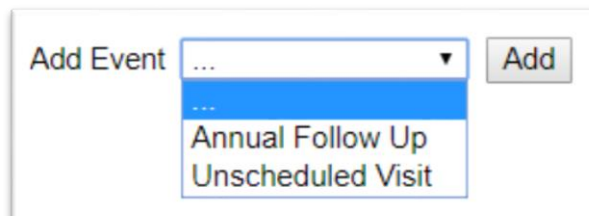
Please complete all forms within each Unscheduled visit.

For the required procedures at each visit please refer to Appendix 1.

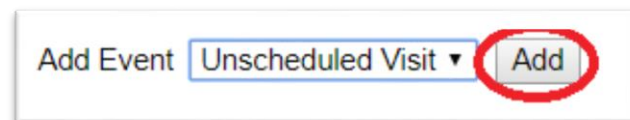
Each time the subject returns to the study site, the PI (or designee) will solicit and record information about AEs, concomitant medications and therapies. All applicable procedures should be performed including MRI and X-ray (according to PI's decision).

In addition, Unscheduled Visit should be added if the subject has undergone a surgical procedure on the treated knee (see details below).

To add an Unscheduled Visit use the 'Add Event' button at the subject level tab:

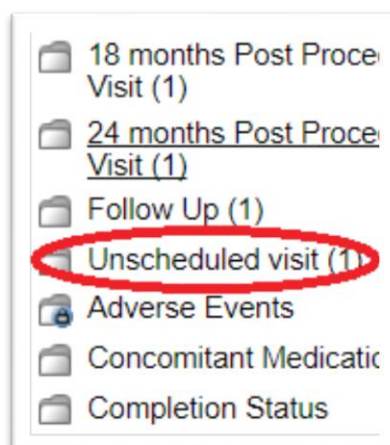


The screenshot shows a web interface with a label 'Add Event' followed by a dropdown menu. The dropdown menu is open, showing two options: 'Annual Follow Up' and 'Unscheduled Visit'. To the right of the dropdown is an 'Add' button.



The screenshot shows the same web interface, but now 'Unscheduled Visit' is selected in the dropdown menu. The 'Add' button is circled in red.

The Unscheduled Visit folder will appear in the subject's matrix:



The screenshot shows a list of folders in a subject's matrix. The folders are: '18 months Post Proce Visit (1)', '24 months Post Proce Visit (1)', 'Follow Up (1)', 'Unscheduled visit (1)', 'Adverse Events', 'Concomitant Medicatic', and 'Completion Status'. The 'Unscheduled visit (1)' folder is circled in red.

9.1. DATE OF VISIT – UNSCHEDULED VISIT

Please remember to update the date of visit.

9.2. UNSCHEDULED VISIT FORM

Reason for the Unscheduled visit	All the relevant reasons should be ticked.
Adverse Event/Adverse Event Follow Up	If ticked, the Adverse Events log (Adverse Events folder) should be updated.
Change in Concomitant Medications	If ticked, the Concomitant Medications log (Concomitant Medications folder) should be updated.
Surgical intervention in the Treated Knee	If ticked: <ul style="list-style-type: none">• The 'Cartilage Repair Assessment' form will be added to the Unscheduled Visit folder and should be updated.• The Adverse Events log (Adverse Events folder) should be updated.
MRI according to CartiHeal protocol	Tick if MRI was performed during the Unscheduled Visit.
Weight bearing AP & Lateral X-ray	Tick if X-Ray was performed during the Unscheduled Visit.
Other diagnostic tests	If ticked, a specification should be provided in the text box below.

9.3. CARTILAGE REPAIR ASSESSMENT (if applicable)

The Cartilage Repair Assessment Form should be updated in case a surgical procedure was performed on the operated knee.

NOTE: the data should be provided for the treated lesions only and in accordance with the number of treated lesions (in 'Knee Evaluation and Concomitant Treatment' form).

For each treated lesion please specify the **Lesion Location**.

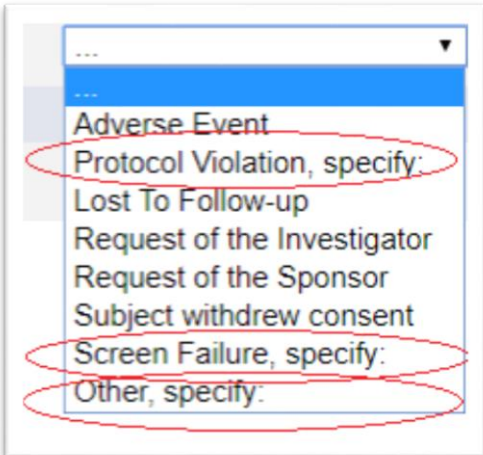
All questions related to a specific lesion are mandatory.

10. COMPLETION STATUS

The 'End of Study' form can be accessed via the Completion Status folder at any stage of the study.

Once the subject is discontinued from the study, the 'End of Study' form should be updated, regardless of the study stage.

Please refer to Appendix 2 for the Study Flowchart.

<p>Did the subject complete the study according to protocol?</p>	<p>Select 'Yes' if the subject has completed the '24 months Post Procedure' Visit and the 'Annual Post-24 Months' Visits (if applicable).</p> <p>Select 'No' if subject was prematurely discontinued from the study (for any reason).</p> <p>NOTE: for each <u>randomized</u> subject, 'Major Violations' form should be updated <u>by the Sponsor</u> prior to subject's study completion (the form is not available for the site). If the 'Major Violations' form was not completed by the sponsor before the 'End of Study' form was updated and saved, a query will be generated by the system upon the 'End of Study' form saving, instructing the site to contact the sponsor. The query may remain open until the issue is resolved. It will not interfere with the 'End of Study' form completion.</p>
<p>Date the subject completed or was discontinued from the study:</p>	<p>Full date is required.</p>
<p>If the subject was prematurely discontinued from the study, please provide the primary reason</p>	<p>One option should be selected from the dropdown list.</p> <p>Some of the options require a specification (mentioned specifically)</p> 

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Primary reason for discontinuation = Adverse Event	An additional question will be added: "Please specify the Adverse Event" – the specified Adverse Event must be consistent with the Adverse Events log.
Primary reason for discontinuation = Lost To Follow-up	An additional question will be added: "Date of Last Contact"

APPENDIX 1 – STUDY SCHEDULE

Procedures	Screening Visit	Final Screening/ Procedure Visit	2 week Post- Procedure Visit (± 1.5 weeks)	3 ^u , 6 ^u , 12 and 18 Months Post- Procedure Visit (± 8 weeks)	24 Months Post- Procedure Visit (± 8 weeks)	Annual Post-24 months Visit ^s (12 months ± 8 weeks)	Unscheduled Visit
Number of Visit	Visit 1	Visit 2	Visit 3	Visits 4-7	Visit 8	Visits 9+	
Obtain Informed Consent	X						
Assignment of Subject Number	X						
Review Inclusion/ Exclusion criteria	X	X (intra operative)					
BMI	X [@]						
Medical History	X						
Baseline MRI	X [*]						
MRI according to CartiHeal protocol				X ^{**}	X ^{**}		X ^{***}
Defect Fill Evaluation according to MRI, off-site				X ^{*,∞}	X ^{**}		
Baseline standing X-ray (AP & Lateral)	X [*]						
Weight bearing AP & Lateral X-ray			X [#]	X [∞]	X		X ^{***}
IKDC Knee Examination form 2000 (Surgeon)	X			X [∞]	X		X
OA Classification Kellgren-Lawrence score, off-site	X						
ICRS Cartilage Injury Standard Evaluation Form 2000 (Subject)	X						
ICRS Knee History Registration (Surgeon)	X						
SF-12 v2	X			X [∞]	X	X	
2000 IKDC Subjective Knee Evaluation Form	X			X [∞]	X	X	
KOOS Subscales	X			X [∞]	X	X	
Tegner score	X			X [∞]	X	X	

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Procedures	Screening Visit	Final Screening/ Procedure Visit	2 week Post-Procedure Visit (± 1.5 weeks)	3 ^μ , 6 [^] , 12 and 18 Months Post-Procedure Visit (± 8 weeks)	24 Months Post-Procedure Visit (± 8 weeks)	Annual Post-24 months Visit ^{\$} (12 months ± 8 weeks)	Unscheduled Visit
mICRS cartilage injury mapping and classification		X					
Arthroscopy and randomization		X					
Analgesic, anti-inflammatory and prescription medicine recording	X	X	X	X	X	X	X
AEs/SAEs		X	X	X	X	X	X
Tissue biopsy with histology							X****
Video recording		X					X

@ Weight and Height, only at screening

X-ray may be performed lying down or standing, per patient comfort

* Screening MRI and X-ray must not be older than 1 year** MRI and Defect Fill evaluation is performed at 12 and 24 months. Additionally, MRI will be performed at 3 and 6 months to an initial cohort of at least 25 patients per study groups

*** MRI and X-ray will be performed according to PI decision

**** According to PI decision if surgery is performed. The biopsy will be sent to a central lab.

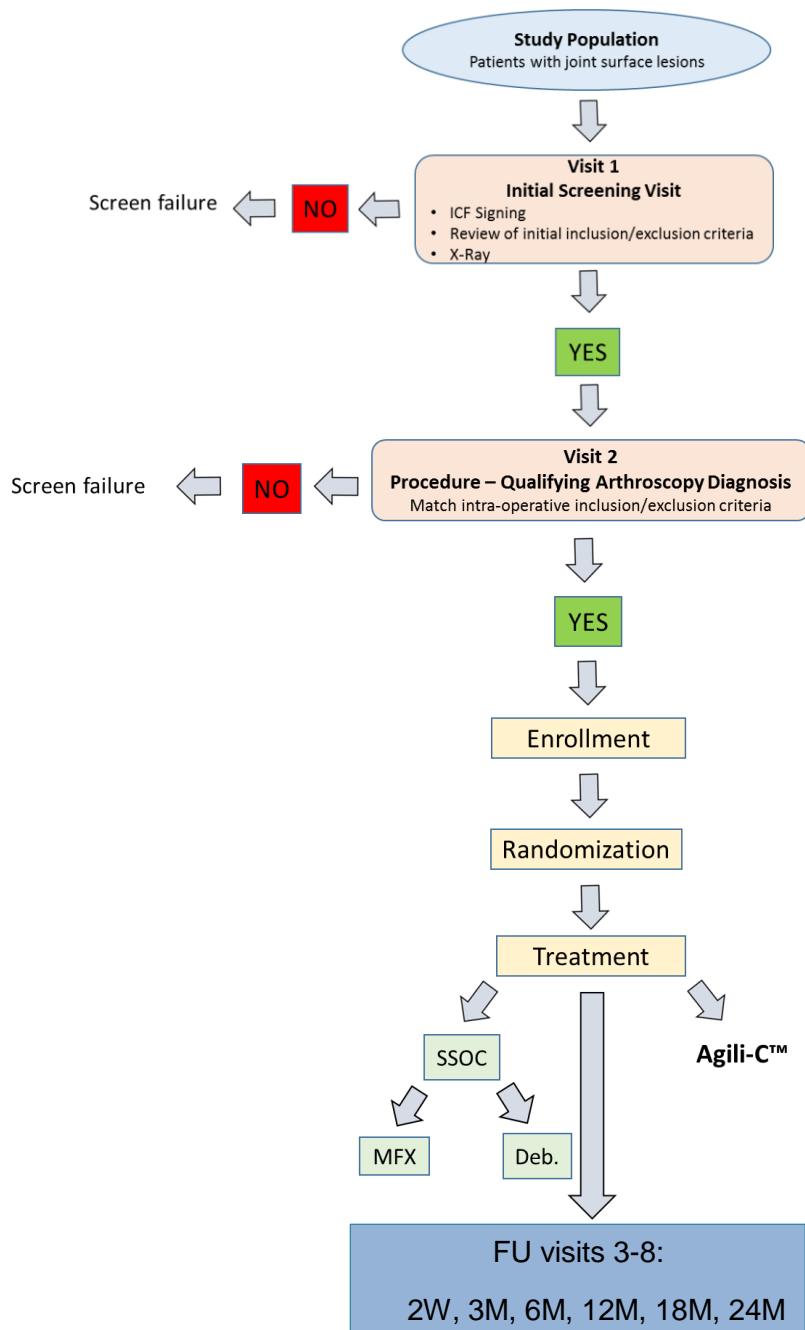
\$ Annual visit until last patient out

^μ The 3 month visit may take place ±2 weeks

[^] The 6 month visit may take place ±4 weeks

[∞] Not applicable for the 3 months visit

APPENDIX 2 – STUDY FLOWCHART



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For any issues, email helpdesk@mdsol.com, visit our [Help Center](#) for self service, or use the [Support contacts](#) below to contact us with any product support needs.

For service in English

Toll-free

1-866-MEDIDATA (633-4328)

Direct number

1-973-659-6780

Toll-free fax

1-877-743-2350

Direct fax

1-973-954-5621

Email

helpdesk@mdsol.com

Hours

24 hours a day, 7 days a week

To find the toll-free number for your location, follow the link below:

<https://www.mdsol.com/en/contact>