MAXIMUM ULNAR CMAP PROTOCOL FOR USE IN MULTICENTER CLINICAL STUDIES AND TRIALS

INTRODUCTION

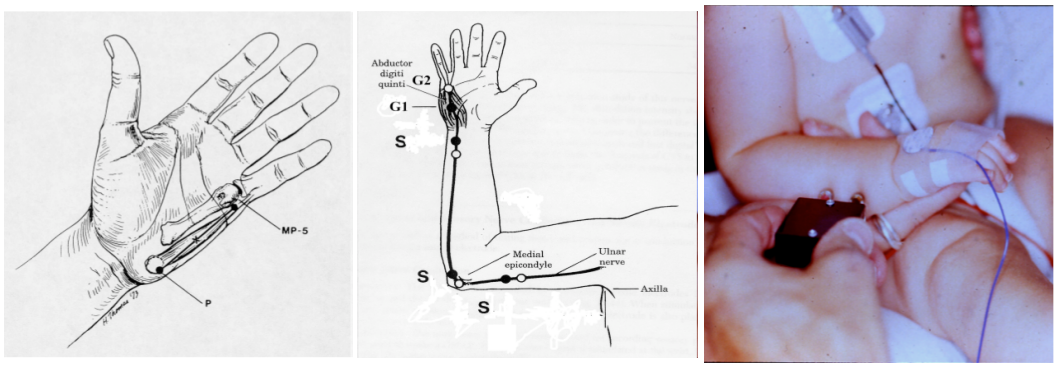
CMAP evaluation is to be performed on every patient at each study visit. MUNE evaluation is to be performed at sites where a neurophysiologist or trained evaluator is available to perform the studies (separate protocol). Two baseline assessments will be obtained at the S1 and S2 visits when possible to collect test-retest data. We will use data only from those children for whom at least 3 separate G1 electrode placements with adequate waveform collections have been performed for the maximum CMAP studies. Five separate G1 electrode placements are the ideal minimum. If additional attempts are made because waveform integrity is compromised by artifact, the best five waveforms should be recorded. Please see additional bolded comments below re: appropriate scoring of CMAP waveforms on the CRF document. All waveforms will be printed and included with the CRF document. All waveforms will undergo central review at the Data Coordinating Center by either Dr. Kathryn Swoboda or Mark Bromberg. This mandatory review will include documentation of minimum number of waveforms collected, limitation of artifact, accurate placement of markers, and accurate recording of values on the CRF document, prior to entry into the database. All sites are required to send a video documenting their technique on 3 subjects, attend a live training session or undergo site visit for live audit at least once yearly, to ensure rigorous attention to the protocol below, to ensure integrity of the collected data.

Documentation of normal limb temperature

Since temperature can affect maximum CMAP amplitude, temperature greater than 33 degrees centigrade should be documented prior to preparation of skin for electrode placement. Temperature should be measured using a surface probe on the lateral aspect of the hand just proximal to the fifth digit. If temperature is less than 33 degrees centigrade, a chemical warming pack or other warming mechanism should be used prior to collecting data.

Preparation of skin and electrode and stimulator placement

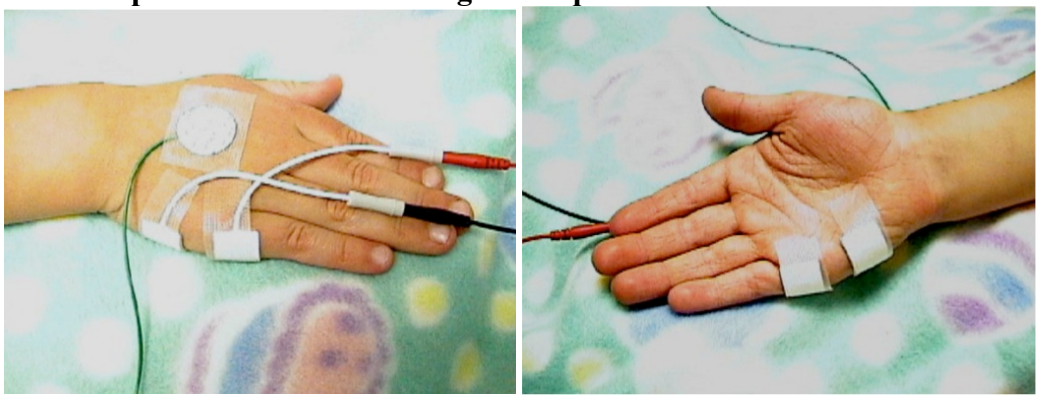
The skin over the ulnar aspect of the palm, the back of the hand, the volar aspect of the wrist are cleaned with alcohol to remove any sweat, lotion or oil. This is very important in SMA patients as they tend to sweat excessively, to limit stimulus artifact obscuring take-off of CMAP waveforms, particularly those of diminished amplitude. Electrode placement is similar to that for standard ulnar motor studies. The G1 primary recording electrode is placed over the motor point of the abductor digiti minimi muscle in the hand, with the first G1 electrode placement at the midpoint of the line drawn between the ulnar aspect of the fifth metacarpophalangeal joint (MP-5) and the ulnar aspect of the pisiform bone (P) in the hand. The G2 reference electrode is placed at the base of the fifth proximal phalanx where it intersects with the MP-5 joint. An adhesive ground electrode is placed on the back of the hand.



Panel 1: Modified figure from "Anatomic Guide for the Electromyographer" Charles C. Thomas, Publisher, 1980, p4.
Panel 2: Modified figure from "Clinical Electromyography Nerve Conduction Studies" Shin J. Oh, Williams and Wilkins, 1993, p195.

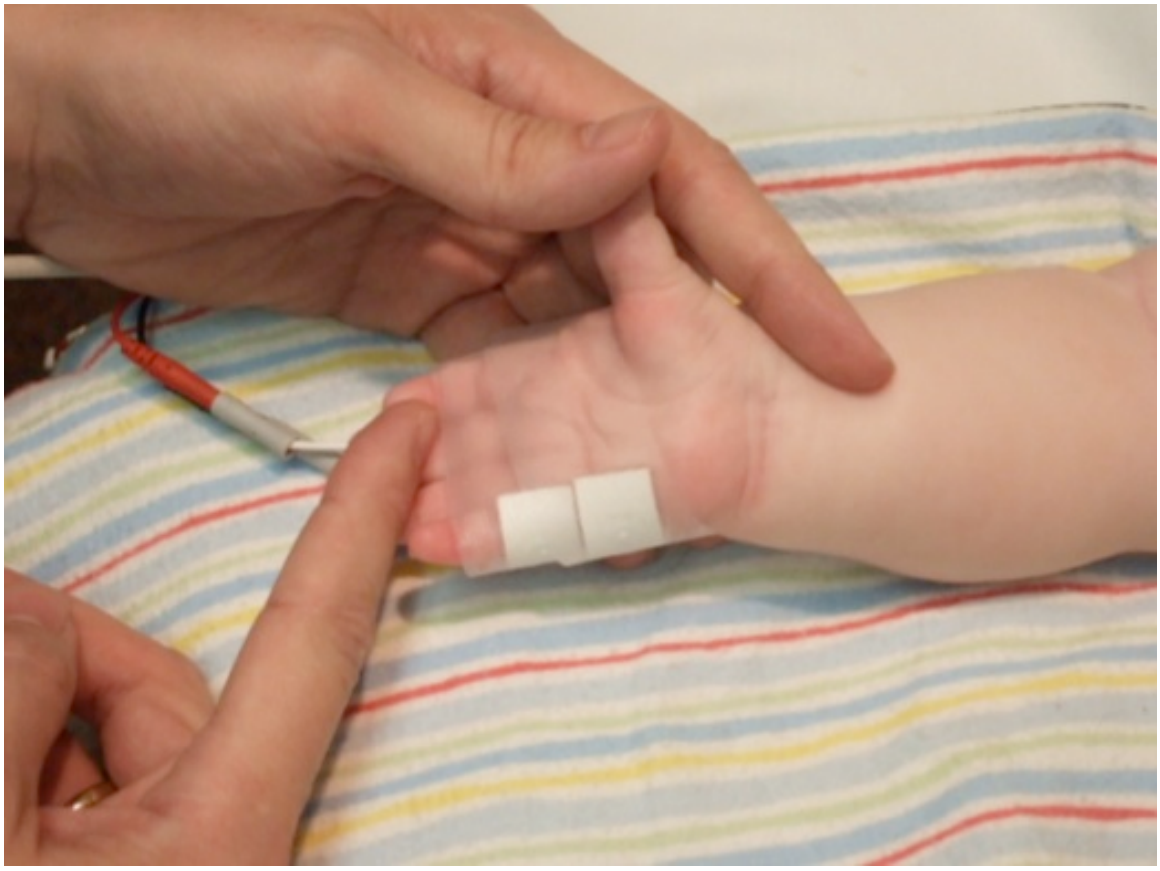
For affected infants and children, it is important to place them in the position most comfortable for them, probably on their back or side. Distraction of attention from the procedure is extremely helpful to enable the most efficient collection of reliable data. Use of a portable DVD player with battery backup is extremely helpful in this context, and parents are encouraged to bring their child's favorite DVDs along. Alternatively, providing music, bubbles or other distractions are helpful. In general, it is helpful to engage parents in distracting the infant or young child. The coordinator or nurse can help assist, but should remain alert to the child's overall state with regard to handling of secretions and oxygenation. The evaluator will need assistance in distraction for the infant so that he or she can remain intent on getting the necessary data as efficiently as possible.

Electrode placement and recording techniques:

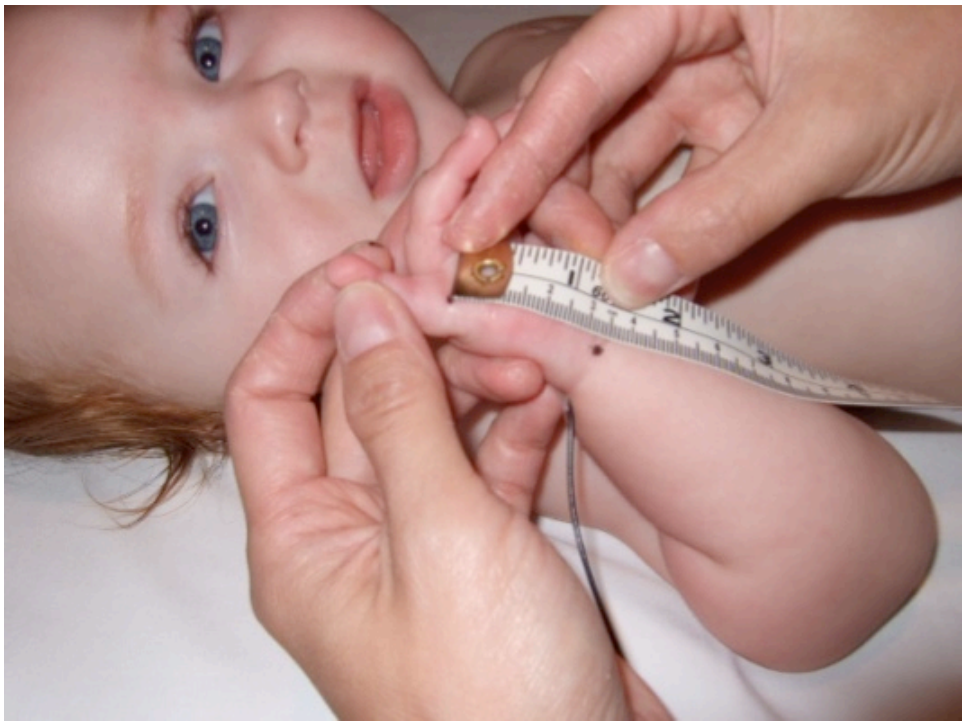


We recommend the use of disposable non-gelled recording electrodes with a silver-silver chloride sensor, and a recording area of 7 x 4 mm. For the CARNIVAL and CARNIVAL TYPE I studies, we used part number 9013L0203, from Alpine Biomedical Neurodiagnostics Accessories; however, this same eletrode configuration is available from several other companies. It is important to maintain consistency of the EMG machine and recording electrodes between visits when comparing data over time in the same patient. The relatively small recording area of this electrode configuration allows

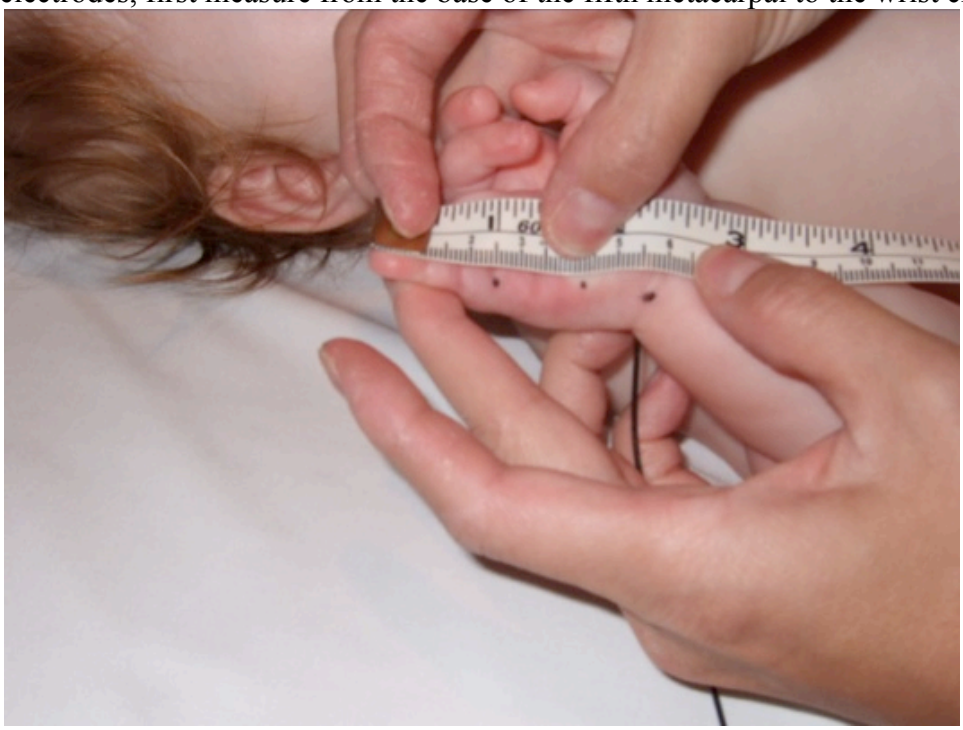
its use in a wide range of settings from small infants to adults, and the sides can be easily trimmed on either side of the recording surface without affecting electrode recording characteristics. Because of excessive sweating and the need to clean and reapply surface electrodes, pre-gelled electrodes are much less desireable. Use of non-gelled electrodes allows them to be gently cleaned with alcohol, after which a small amount of gel can be reapplied and reused throughout the study as the G1 placement is varied (use in infant demonstrated below). It is helpful in this setting to have adhesive tape to help secure the electrodes given the excessive sweating; we have found that transpore 3M tape works very well for this purpose, since electrodes quickly lose their self-adhesive properties when they are moved from site to site.



The ground can be placed on the dorsum of the hand, as in older subjects (above). In the lower photos, note relatively large size of electrodes on smaller hand size of type 1 infant – certain electrodes in which the recording surface area is clearly delineated can be trimmed on either side of the actual recording interface. The type of round disposable electrode used as a ground electrode in the photo above can also be used as a recording electrode. However, use consistent electrode size and types for all evaluations in an individual subject.

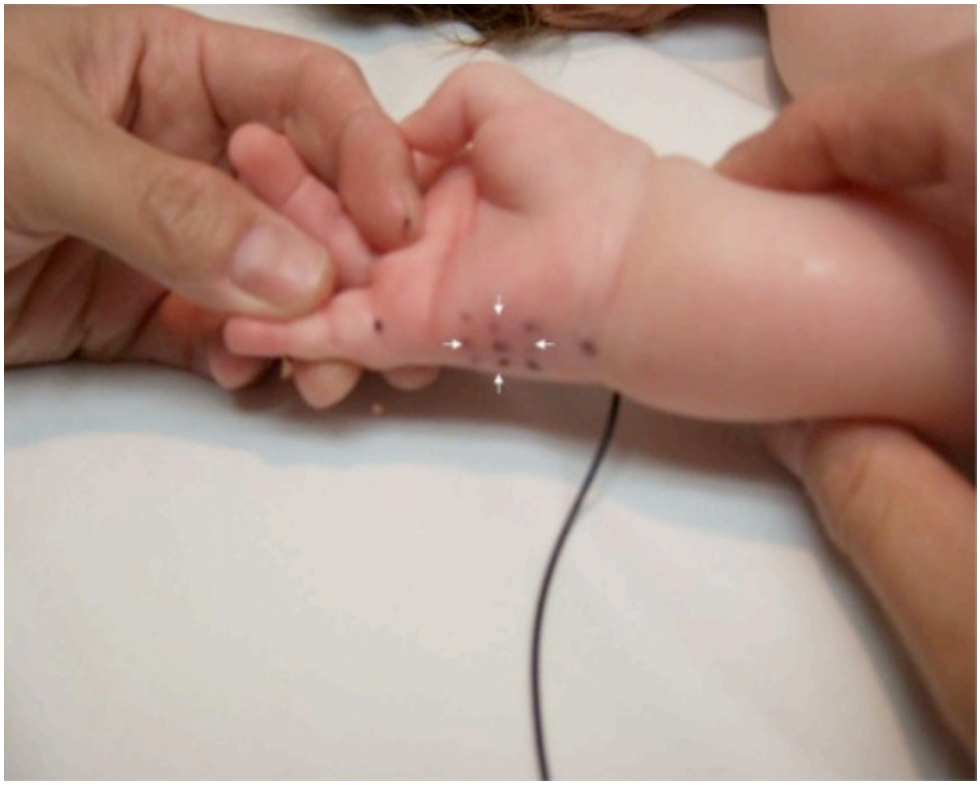


In an infant or smaller child, for proper placement of recording (G1) and reference (G2) electrodes, first measure from the base of the fifth metacarpal to the wrist crease.



Make an ink mark at the base of the fifth metacarpal for placement of the G2 electrode. It will remain at this site during all movements of the G1 electrode to try to ascertain the

maximum motor point. Make another mark at the wrist crease, then mark a point 2/3 of the way from the base of the fifth metacarpal towards the wrist crease. This middle mark indicates the appropriate place for your first G1 electrode placement



You can make additional marks to indicate placement points to help guide you in moving the G1 electrode. Remember that often the bulk of the adductor digiti mimini muscle is somewhat posterior to a line transecting the ventral/dorsal meridian. In addition to a recorded response at the first mark, move the recording electrode at least four additional times to collect five distinct maximum CMAP waveforms, as indicated by white arrows above.

A maximum ulnar compound motor action potential (CMAP) should be obtained by stimulation at the wrist starting using a stimulus duration of 50 milliseconds and an intensity sufficient to elicit a maximum CMAP (a good starting point for stimulus intensity is usually around 15-20 mA, and the intensity should be further increased in increments of 10- 15% above that until the stimulus intensity which elicits the maximal response is reached). In many infants less than 6 months of age, or in chubby older infants, a stimulus duration of 100 milliseconds is often necessary. An ideal maximum CMAP response should not have an initial positive deflection, although this may be difficult in very weak type I children due to the extremely low amplitude of the response. Recleansing the skin and reapplication of electrodes may be required several times to ensure the best response. If the initial positive deflection exceeds 30% of the maximum

CMAP amplitude, this likely represents a placement that is too far distant from the motor

point; thus, it should not be transferred to the CRF. The G1 electrode should be moved in 1-2 mm increments proximal to the initial placement for ideally, two additional placements, then anterior and posterior to the midline in the plane of the maximum response, for a minimum total of 5 measures to identify a point of maximum CMAP amplitude and negative peak area. A minimum of at least 3 G1 electrode placements is required to use the data for analysis, and 5 G1 electrode placements is optimal. **If the responses are technically unsatisfactory, due to a >30% initial positive deflection compared to the maximum CMAP, or due to electrical impedence resulting in a unstable baseline, the best of those responses from a technical standpoint should be chosen to record on the CRF. If no adequate response could be obtained due to > 30% positive deflection for all waveforms, a 0 should be recorded on the CRF for each insufficient response to total 5. If electrical impedence causing artifact prevents a stable baseline during all attempts to gather data, a line should be drawn through the CRF, and the evaluator should indicate in the comments section re: technical difficulties. The same machine and settings should be used for each study visit. In order to use the data, attempts need to be adequately documented in terms of number in order to use the data and score it appropriately.**

Troubleshooting for electrical interference:

Common causes of an unstable baseline in SMA infants and children include excessive sweating, increased subcutaneous tissue and short distances between the stimulating and recording electrodes. Frequent cleaning of electrodes and recording areas, and reapplication of a small amount of gel may be necessary to record optimal CMAP results in these very weak infants. Each time stimulating electrode is moved, the wrist should again be wiped clean with an alcohol swab and allowed to dry briefly, to prevent bridging. Anything in the room that is plugged into an electrical outlet should be unplugged (don't forget if you use a DVD player to have battery backup). Same is true if child is monitored using pulse oximetry during the study.

Marking the waveforms prior to transfer of data to the CRF:

Once you have collected at least five maximum waveforms from distinct recording sites, print out all waveforms collected, and review carefully to ensure markers for takeoff, negative peak amplitude, and return to baseline are accurately marked. If necessary, adjust markers as needed prior to recording data on the CRF. Then, you may either print out final waveforms to include with your CRF as part of the datafile, or submit final set electronically, ensuring that no more than one waveform for each site is included. Negative peak amplitude (in mV) and negative peak area (in mVms) are recorded for each site; only the five best responses are recorded on the CRF.