Treatment of Apert Syndrome: A Long-Term Follow-Up Study

Karam A. Allam, M.D.
Derrick C. Wan, M.D.
Krit Khwanngern, M.D.
Henry K. Kawamoto, M.D., D.D.S.
Neil Tanna, M.D.
Adam Perry, M.D.
James P. Bradley, M.D.

Los Angeles, Calif.

Background: Patients with Apert syndrome have severe malformations of the skull and face requiring multiple complex reconstructive procedures. The authors present a long-term follow-up study reporting both surgical results and psychosocial status of patients with Apert syndrome.

Methods: A retrospective study was performed identifying patients with Apert syndrome treated between 1975 and 2009. All surgical procedures were recorded and a review of psychosocial and educational status was obtained when patients reached adulthood.

Results: A total of 31 patients with Apert syndrome were identified; nine with long-term follow-up had complete records for evaluation. The average patient age was 30.4 years. Primary procedures performed included strip craniectomy and fronto-orbital advancement. Monobloc osteotomy and facial bipartition were performed in eight patients, and all underwent surgical orthognathic correction. Multiple auxiliary procedures were also performed to achieve better facial symmetry. Mean follow-up after frontofacial advancement was 22.5 years. Psychosocial evaluation demonstrated good integration of patients into mainstream life.

Conclusions: This report presents one of the longest available follow-up studies for surgical correction of patients with Apert syndrome. Although multiple reconstructive procedures were necessary, they play an important role in enhancing the psychosocial condition of the patients, helping them integrate into mainstream life. (Plast. Reconstr. Surg. 127: 1601, 2011.)
tion of midface clefts and adopted by Tessier to correct hypertelorbitism and, more importantly, create a curvature to the flattened Apert facies.\textsuperscript{9,10} Evolution in surgical techniques since these early reports has led to contemporary use of monobloc distraction to minimize postoperative relapse secondary to a tight soft-tissue envelope.\textsuperscript{11–13}

Despite the numerous articles devoted to treating Apert syndrome, no reports of long-term results have been written. This study attempts to fill this void; adult patients with Apert syndrome treated at the University of California, Los Angeles were assessed for long-term skeletal and soft-tissue changes and functional and aesthetic results in relation to the degree to which they were able to socially integrate into mainstream life.

**PATIENTS AND METHODS**

A retrospective study was performed, identifying all patients with Apert syndrome treated by the senior author (H.K.K.) between 1975 and 2009. Because outcomes were evaluated, this study underwent level I review by the institutional review board committee for exempt status. Exclusion criteria were a follow-up period of less than 15 years after frontofacial advancement surgery or incomplete records at the time of review. To be included, patients therefore had to have completed all reconstructive procedures. Not all patients were referred at birth, as some were seen at a later age with or without prior craniofacial interventions.

**Management Protocol**

All patients were seen and followed by a multidisciplinary team, which consisted of a plastic surgeon, neurosurgeon, clinical geneticist, dentist, orthodontist, ophthalmologist, otolaryngologist, pediatrician, speech therapist, audiologist, and social worker. Each patient included in the study was operated on by a single craniofacial surgeon (H.K.K.) and a neurosurgeon. Table 1 shows the management protocol used.

Team follow-up visits were scheduled at least once every 3 to 6 months after each major procedure. Otherwise, check-ups were scheduled annually until late adolescence for those patients who had no functional problems requiring immediate attention. During follow-up visits, patients and their parents were specifically asked about complaints suggestive for elevated intracranial pressure, respiratory problems, ocular problems, and hearing difficulty. Skull circumference was measured and facial features were assessed. Radiographs were obtained when necessary.

**Table 1. Management Protocol for Apert Syndrome**

<table>
<thead>
<tr>
<th>Age</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth–4 mo</td>
<td>Complete multidisciplinary assessment</td>
</tr>
<tr>
<td>4–6 mo</td>
<td>Fronto-orbital advancement surgery</td>
</tr>
<tr>
<td>6 mo–1 yr</td>
<td>Posterior vault expansion, if needed</td>
</tr>
<tr>
<td>2–6 yr</td>
<td>Annual assessment by craniofacial team</td>
</tr>
<tr>
<td>6–7 yr</td>
<td>Monobloc advancement or Le Fort III osteotomy, facial bipartition (if needed), nasal augmentation (if needed)</td>
</tr>
<tr>
<td>6–8 yr</td>
<td>3- to 6-mo checks</td>
</tr>
<tr>
<td>8 yr–teenage</td>
<td>Orthodontics, annual assessment by craniofacial team</td>
</tr>
<tr>
<td>Teenage</td>
<td>Le Fort I osteotomy, BSSO (if needed), genioplasty (if needed)</td>
</tr>
<tr>
<td>Late teenage</td>
<td>Final assessment, revisionary and touch-up procedures</td>
</tr>
</tbody>
</table>

BSSO, bilateral sagittal split osteotomy.

A review of psychosocial and educational status was performed at adulthood after completion of all reconstructive procedures. This was accomplished through either a face-to-face or an over-the-phone interview with patients and their families. Highest level of education completed, relationship status, and work history were all queried.

**RESULTS**

A total of 31 patients with Apert syndrome were identified, seven of whom had less than 15 years’ follow-up after midface advancement surgery; these patients were thus too young and were excluded from the study. Of the remaining 24 patients with follow-up more than 15 years, nine (three men and six women) had complete records and were considered finished cases. The mean age for these nine patients was 30.4 ± 6.5 years (range, 22 to 41 years). The average follow-up after frontofacial advancement surgery was 22.5 ± 6.3 years (range, 15 to 30 years).

Primary procedures to address the cranium consisted of five fronto-orbital advancements and three strip craniectomies. Patients with strip craniectomies were operated on elsewhere before initial evaluation by our team, and all of these were performed between 4 and 6 months of age (average, 4.7 months) (Figs. 1 and 2). [See Figure, Supplemental Digital Content 1, which shows a patient with Apert syndrome at age 10 (above) and at age 40 (below), 30 years after monobloc advancement and facial bipartition, \url{http://links.lww.com/PRS/A304}]. In one patient with pansynostosis, surgical release was performed at 2 weeks of age and repeated at 18 months because of refusion of the sutures. For those undergoing fronto-orbital advancement at the University of California, Los Angeles, the operation was performed at 5 and 9 months of age.
for two patients, and because of later initial presentation, at 4 years and 18 years for two others. When bulging of the temporal bone was noted, this was managed by reversal of bone at the time of fronto-orbital advancement.

Facial bipartition and monobloc advancement were performed in all but one patient; this single patient had a Le Fort III advancement alone, as good forehead projection was already present. In seven patients, facial bipartition was performed concomitantly with monobloc advancement (average age, 7.5 ± 2.7 years; range, 6 to 13 years), and one patient had facial bipartition later in adolescence at 18 years of age following prior monobloc advancement at age 5.

[See Figure, Supplemental Digital Content 2, which shows (left) a 5-year-old boy with Apert syndrome who had strip craniectomy at 4 months of age, before monobloc advancement and facial bipartition, http://links.lww.com/PRS/A305. (Second from left) The same patient at age 18, 13 years after monobloc advancement and facial bipartition. (Second from right) The patient at age 23, after Le Fort I advancement and genioplasty. (Right) The patient at age 35. He underwent a second bilateral sagittal split osteotomy. The progressive soft-tissue deformity is also shown.] All patients who underwent monobloc advancement or Le Fort III advancement had considerable improvement in appearance (Figs. 3 and 4).

The occlusal status was also followed until late adolescence. As expected, with mandibular growth, all patients developed an anterior open bite and class III malocclusion. This malocclusion required a corrective Le Fort I maxillary osteotomy in all nine cases at an average age of 17.7 ± 1.9 years (range, 15 to 21 years). Two patients also underwent bilateral sagittal split osteotomy of the mandible. One was performed simultaneously with the Le Fort I surgery at age 15 and was repeated 1 year later to correct abnormal rotation of the mandible. The second bilateral sagittal split osteotomy was performed at age 34 following original Le Fort I surgery at 21 years of age. (See Figure 2, Supplemental Digital Content 2, http://links.lww.com/PRS/A305.) Osseous genioplasty was performed in three patients (average age, 17.3 ± 3.2 years; range, 15 to 21 years). These were all performed simultaneously with the original Le Fort I procedure. The bony operations are summarized in Tables 2 and 3.

Other auxiliary procedures were also performed on several patients. Nasal reconstruction with split calvarial bone graft to augment the dorsum was performed in seven patients. This was usually performed at the time of midface corrective surgery and repeated later if necessary. Ear cartilage was also harvested to augment the nasal tip in one patient, and in another, septoplasty was performed.

Medial and/or lateral canthopexy was necessary in three patients. Brow lifting was performed in two patients and frontalis scoring or resection was performed in three. In addition, two patients had their corrugator muscles resected. Removal of temporal fat pads was also necessary in two patients. The soft-tissue procedures are summarized in Table 4.

Complications

Complications observed during follow-up included a persistent bone defect in the cribriform area after monobloc operation in one patient. This resulted in development of an encephalocele, necessitating an intracranial approach to repair the defect with calvarial bone grafting. One patient had a cerebrospinal fluid leak postoperatively that resolved following close observation. Bony defects and contour irregularities in the forehead, maxilla, malar area, orbital rim, and/or temporal regions were noted in three patients. Reconstruction was accomplished using a variety of approaches, with priority given to calvarial bone graft (n = 1), followed by rib graft (n = 1), and lastly synthetic materials (hydroxyapatite). These were used for forehead and temporal augmentation in two cases, with or without autogenous bone. Fat injection was also used to reduce contour irregularities and augment the malar region in two patients. This technique has been adopted on more recent patients, and we now favor the use of fat for even minor contour irregularities.

Psychosocial Evaluation

Of the eight patients whom we could assess for social and educational progress, five had been enrolled in regular education and three received special education. Three patients received college degrees, another three had completed some college, and the remaining two graduated from high school. All but one patient reported a normal social life with several friends; the eighth patient reported being shy and socially isolated, with no friends. One patient married, one reported being in a relationship, and the remainder were all single. None have had children. Three patients reported having jobs and were currently doing very well at work.
Fig. 1. (Above) A 6-year-old Apert patient with a history of strip craniectomy at the age of 4 months. (Center) The patient at age 6 years, immediately after monobloc advancement and facial bipartition. (Below, left) Occlusion of the patient at the same age, before monobloc advancement. (Below, right) Occlusion after monobloc advancement and facial bipartition.
Fig. 2. (Above) The patient shown in Figure 1, at age 16, 10 years after monobloc surgery. (Center) The patient at age 22, after Le Fort I surgery. (Below, left) The patient at age 16. Note the class III malocclusion before orthognathic surgery. (Below, right) Note the class I occlusal relationship after Le Fort I surgery.
DISCUSSION

Despite tremendous technical advances over the past half century, surgical management of patients with Apert syndrome remains a complex challenge. Aesthetic outcomes are frequently suboptimal. To the best of our knowledge, this present report is the longest longitudinal study evaluating skeletal stability and final functional, aesthetic, and psychosocial aspects for patients with Apert syndrome. The mean follow-up after frontofacial advancement was 22.5 years, 12.8 years after the final operation.

Controversy remains surrounding surgical correction of vault deformities in early infancy versus later in childhood. Our experience with calvarial remodeling and postoperative reossification suggests that operations can be performed before 6 months of age without any significant increase in sutural refusion. In addition, we prefer to correct the turricephaly at the same time.

Fig. 3. (Left) An 8-year-old girl with Apert syndrome with no prior history of release. Note the severity of forehead and midface retrusion and degree of exophthalmos. (Right) The patient at age 10, 2 years after monobloc advancement, facial bipartition, and nasal reconstruction with cranial bone graft.
### Table 2. Patient Age at the Time of Vault and Midface Procedures

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Frontofacial Advancement Follow-Up (yr)</th>
<th>Strip Craniectomy</th>
<th>Fronto-Orbital Advancement</th>
<th>Monobloc Osteotomy (yr)</th>
<th>Le Fort III Osteotomy</th>
<th>Facial Bipartition (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>30</td>
<td>6 mo</td>
<td>No</td>
<td>10</td>
<td>No</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>16</td>
<td>No</td>
<td>5 mo</td>
<td>6</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>29</td>
<td>No</td>
<td>4 yr</td>
<td>No</td>
<td>8 yr</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>19</td>
<td>No</td>
<td>9 mo</td>
<td>6</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>15</td>
<td>No</td>
<td>13</td>
<td>No</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>16</td>
<td>4 mo</td>
<td>No</td>
<td>6</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>25</td>
<td>No</td>
<td>8</td>
<td>No</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>22</td>
<td>2 wk and 18 mo</td>
<td>18 yr</td>
<td>6</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>30</td>
<td>4 mo</td>
<td>No</td>
<td>5</td>
<td>No</td>
<td>18</td>
</tr>
</tbody>
</table>

**Fig. 4.** (Left) The same patient as shown in Figure 3, at age 18, before Le Fort I surgery. (Right) The patient at age 33, 25 years after monobloc facial bipartition surgery.
time, which further reduces the volume of space created by the fronto-orbital advancement. Alternative approaches exist, including spring-assisted remodeling, but these novel developments are still controversial and have yet to be definitively proven to be superior to fronto-orbital advancement and vault remodeling. Early in our series, bony fixation was achieved using wires; this was later changed to titanium plates and screws. Presently, we use biodegradable plates and screws. This change toward biodegradable fixation was made because of observed translocation of extracranial metallic implants with continued growth of the calvarium.23

In our study, both patients who underwent fronto-orbital advancement in infancy at the University of California, Los Angeles required subsequent procedures for forehead recession. This finding is consistent with other reports that have shown a reoperation rate as high as 95 to 100 percent.14,15 The problem of fronto-orbital relapse may be secondary to the underlying genetic defect and tight soft-tissue envelope.14 Also of note, neither of our patients undergoing fronto-orbital advancement in infancy required a subsequent posterior vault expansion that would have been indicated had a Chiari malformation or inadequate correction of turricephaly been observed.

During early childhood, both forehead recession and midface retrusion contribute to functional (e.g., obstructive sleep apnea, exorbitism, and exposure keratitis) and aesthetic considerations. Monobloc advancement plus asymmetric facial bipartition is our operation of choice to correct both the forehead and midface deformity. If midface deformity is present without forehead recession, a subcranial Le Fort III procedure is preferred. In our series, the average age for monobloc advancement and facial bipartition was 7.5 years. Because of later presentation, monobloc advancement was performed at 13 years of age for one patient and secondary facial bipartition was performed in another at 18 years because of a gap in follow-up. Although parents may wish to correct these deformities as early as possible and some surgeons may advocate an initial midface advancement between 4 and 6 years of age in anticipation of school, we prefer to wait until the age of early mixed dentition (6 to 7 years) for several reasons.1,10 At this age, the vault and orbits have attained 85 to 90 percent of their adult size and the permanent central maxillary incisors have erupted.24,25 The brain of the young child is also capable of rapidly expanding to fill the surgically created space, which may not always be the case as the child ages.26,27 Computed tomographic studies of extradural dead space following fronto-orbital surgery have demonstrated that although older children and adults may retain the capacity to obliterate dead space, this may occur in a much more delayed fashion.26 Lastly, young children have yet to fully pneumatize the frontal sinuses, obviating many concerns regarding infection if monobloc advancement were performed at a later age.28 The frontal sinus, when present, is small at the time of monobloc facial bipartition, and we have yet to observe the development of a frontal mucocele over the past 35 years.

Facial bipartition to correct asymmetric hypertelorbitism was performed concomitantly with

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**Table 3. Patient Age at the Time of Orthognathic/Forehead/Nose/Chin Procedures**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Le Fort I Osteotomy (yr)</th>
<th>First BSSO</th>
<th>Second BSSO</th>
<th>Genioplasty</th>
<th>Nasal Augmentation with BG</th>
<th>Hydroxyapatite Augmenting Forehead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>No</td>
<td>16</td>
<td>No</td>
<td>1 (10 yr)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>15 yr</td>
<td>16</td>
<td>15 yr</td>
<td>5 (8, 19, and 20 yr)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>No</td>
<td>16</td>
<td>No</td>
<td>2 (6 and 16 yr)</td>
<td>16 yr</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>No</td>
<td>16</td>
<td>No</td>
<td>1 (14 yr)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>No</td>
<td>16</td>
<td>No</td>
<td>2 (10 and 18 yr)</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>No</td>
<td>16</td>
<td>No</td>
<td>3 (18, 19, and 23 yr)</td>
<td>19 yr</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>No</td>
<td>16</td>
<td>No</td>
<td>3 (18, 19, and 21 yr)</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>No</td>
<td>21</td>
<td>34 yr</td>
<td>21 yr</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>34 yr</td>
<td>34</td>
<td>34 yr</td>
<td>21 yr</td>
<td>No</td>
</tr>
</tbody>
</table>

BSSO, bilateral sagittal split osteotomy; BG, bone grafting.

**Table 4. Soft-Tissue Operations**

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>No. of Patients</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palatoplasty</td>
<td>2</td>
<td>1 and 2</td>
</tr>
<tr>
<td>Pharyngoplasty</td>
<td>2</td>
<td>7 and 10</td>
</tr>
<tr>
<td>Medial canthopexy</td>
<td>2</td>
<td>8 and 19</td>
</tr>
<tr>
<td>Lateral canthopexy</td>
<td>3</td>
<td>8, 19, and 19</td>
</tr>
<tr>
<td>Creation of palpebral fissure</td>
<td>2</td>
<td>7 and 19</td>
</tr>
<tr>
<td>Brow lift</td>
<td>2</td>
<td>16 and 20</td>
</tr>
<tr>
<td>Frontalis myotomy and corrugator resection</td>
<td>3</td>
<td>16, 19, and 20</td>
</tr>
<tr>
<td>Temporal fat pads resection</td>
<td>2</td>
<td>16 and 18</td>
</tr>
<tr>
<td>Fat transfer</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Ear cartilage to nose</td>
<td>2</td>
<td>19 and 20</td>
</tr>
<tr>
<td>Septoplasty</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>
monobloc advancement in our series. This also allowed for correction of the flattened facial curvature through bending of the face and widening the narrow maxillary alveolar arch. Bipartition, however, may result in orbital sequelae, including eyelid contour irregularities and ptosis. In our patients, several minor procedures were performed to achieve acceptable eyelid shape and position. These procedures included brow lift, medial and/or lateral canthopexy, creation of a superior palpebral fold, frontalis myotomy, and corrugator resection.

Overcorrection of midface advancement was performed at the occlusal level to compensate for the growing mandible, as significant midfacial growth was not expected. In addition, correction of orbital asymmetry often created a posterior open bite on the side with the lower orbit. This space closed rapidly without treatment, however, and correction of any malocclusion was therefore deferred. Importantly, the primary goal of monobloc and facial bipartition was to correct the upper part of the face. Occlusion was a distant secondary consideration and must await the completion of facial growth. After long-term follow-up, we found frontofacial advancement to be stable, as only one patient required a secondary fronto-orbital advancement at the age of 18 years.

The development of life-threatening complications following either monobloc or facial bipartition has generally been attributed to the presence of extradural dead space and communication between the anterior cranial fossa and nasal cavities. In our series, one serious complication in the form of orbital asymmetry often created a posterior open bite on the side with the lower orbit. This space closed rapidly without treatment, however, and correction of any malocclusion was therefore deferred. Importantly, the primary goal of monobloc and facial bipartition was to correct the upper part of the face. Occlusion was a distant secondary consideration and must await the completion of facial growth. After long-term follow-up, we found frontofacial advancement to be stable, as only one patient required a secondary fronto-orbital advancement at the age of 18 years.

Surgical advancement of the midface in children with Apert syndrome does not induce normal midface growth thereafter. With continued mandibular growth and development, an anterior crossbite/class III malocclusion is usually inevitable. Le Fort I osteotomy with or without bilateral sagittal split osteotomy was therefore necessary to correct the dentoalveolar discrepancy and occlusal disharmony in all patients.

An obtuse nasofrontal angle and flat nasal dorsum accentuate the concave facial profile caused by midface retrusion in patients with Apert syndrome. A more normal nasofrontal angle was achieved by advancing the supraorbital bar during infancy. In our patients, augmentation of the nasal dorsum later in childhood was also often needed. To accomplish this, a split calvarial bone graft was inserted at the time of frontofacial advancement. This, however, needed to be repeated in some, as the lack of growth in the bone graft or resorption secondary to a tight overlying soft-tissue envelope yielded suboptimal results.

Prominence in the region of the temporal fossa is another problem commonly noted in patients with Apert syndrome. Prior reports have documented bilateral hyperplasia of the superficial temporal fat pads, and this has been treated with surgical contouring. We observed temporal fat pad hyperplasia in two of our patients, both of whom required resection.

Evaluation of an adult patient with Apert syndrome would be incomplete without looking at psychosocial outcomes. Tragically, children were once routinely institutionalized and outcast from society before the introduction of contemporary reconstructive techniques. Tessier wrote that his patients were “considered to be monsters, as such are hidden by their families or shunned in institutions by society.” Modern approaches have enabled these children to better integrate into mainstream society. Although Apert syndrome has historically been associated with mental retardation, early interventions that allow for brain growth may result in greater intellectual development.

Despite recognition of the potential for normal intelligence in children born with Apert syndrome, multiple factors converge to maintain uniform stigmatization and erroneous designation as developmentally delayed. These variables include persistent societal expectation that facially disfigured individuals are of subnormal intelligence and the self-misjudgment of intelligence and capacity by the disfigured patient. Researchers have studied the psychological adjustment in children with Apert syndrome before and after reconstructive procedures. Importantly, they have shown that a child’s self-esteem improved significantly following surgical intervention.

This present report demonstrates that patients with Apert syndrome can function quite well in society. They can achieve a high level of education, hold full-time employment, and integrate well socially. As for relationships, one patient eventually married and another reported dating. The remaining patients were still single. Importantly, all but one had several friends and felt well accepted by their peers.
CONCLUSIONS

This comprehensive review of nine patients with Apert syndrome represents one of the longest follow-up reports for surgical reconstruction. In our evaluation of results, several key points have been highlighted. Importantly, reconstructive procedures should be correlated with facial growth and development. Although fronto-orbital advancement and posterior vault correction—if necessary—can be accomplished before 1 year of age, monobloc advancement and facial bipartition should not be performed until age 6 or 7. Also, although patients in this report underwent conventional monobloc advancement, we have now adopted the use of internal distracters. When performing monobloc and facial bipartition with distraction, it is particularly instructive to pay attention to facial asymmetry and curvature, as facial bending with these procedures allows for amelioration of the flattened face. To correct occlusion, a Le Fort I procedure with or without sagittal split rateration of the flattened face. To correct occlusion, a Le Fort I procedure with or without sagittal split

REFERENCES


Instructions for Authors: Update

Registering Clinical Trials

Beginning in July of 2007,PRS has required all articles reporting results of clinical trials to be registered in a public trials registry that is in conformity with the International Committee of Medical Journal Editors (ICMJE). All clinical trials, regardless of when they were completed, and secondary analyses of original clinical trials must be registered before submission of a manuscript based on the trial. Phase I trials designed to study pharmacokinetics or major toxicity are exempt.

Manuscripts reporting on clinical trials (as defined above) should indicate that the trial is registered and include the registry information on a separate page, immediately following the authors’ financial disclosure information. Required registry information includes trial registry name, registration identification number, and the URL for the registry.

Trials should be registered in one of the following trial registries:

- http://www.clinicaltrials.gov/ (Clinical Trials)
- http://actr.org.au (Australian Clinical Trials Registry)
- http://isrctn.org (ISRCTN Register)
- http://www.trialregister.nl/trialreg/index.asp (Netherlands Trial Register)
- http://www.umin.ac.jp/ctr (UMIN Clinical Trials Registry)